

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
8 March 2001 (08.03.2001)

PCT

(10) International Publication Number  
**WO 01/16318 A2**

- (51) International Patent Classification<sup>7</sup>: C12N 15/12, C07K 14/47, 14/705, G01N 33/53, C12N 15/62, C07K 16/18  
PCT/US00/04414  
22 February 2000 (22.02.2000) US  
PCT/US00/05601 1 March 2000 (01.03.2000) US  
60/187,202 3 March 2000 (03.03.2000) US  
60/191,007 21 March 2000 (21.03.2000) US  
PCT/US00/08439 30 March 2000 (30.03.2000) US  
60/199,397 25 April 2000 (25.04.2000) US  
PCT/US00/14042 22 May 2000 (22.05.2000) US  
60/209,832 5 June 2000 (05.06.2000) US
- (21) International Application Number: PCT/US00/23328
- (22) International Filing Date: 24 August 2000 (24.08.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (71) Applicant (*for all designated States except US*): GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).
- (30) Priority Data:  
PCT/US99/20111  
1 September 1999 (01.09.1999) US  
PCT/US99/21090  
15 September 1999 (15.09.1999) US  
60/169,495 7 December 1999 (07.12.1999) US  
60/170,262 9 December 1999 (09.12.1999) US  
60/175,481 11 January 2000 (11.01.2000) US  
PCT/US00/04341  
18 February 2000 (18.02.2000) US  
PCT/US00/04342  
18 February 2000 (18.02.2000) US
- (72) Inventors; and  
(75) Inventors/Applicants (*for US only*): EATON, Dan, L. [US/US]; 75 Knight Drive, San Rafael, CA 94901 (US). FILVAROFF, Ellen [US/US]; 538 18th Avenue, San Francisco, CA 94121 (US). GERRITSEN, Mary, E. [CA/US]; 541 Parrott Drive, San Mateo, CA 94402 (US). GODDARD, Audrey [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). GODOWSKI, Paul, J. [US/US]; 2627 Easton Drive, Burlingame, CA 94010 (US). GRIMALDI, Christopher, J. [US/US]; 1434 36th

[Continued on next page]

(54) Title: SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

<subunit 1 of 1, 266 aa, 1 stop  
<MW: 29766, pI: 8.39, NX(S/T): 0  
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AVLCIATIIYVRYKQVHALSPEENVIIKLNKAGLVGLSCLGLSIVANFQKTTLFAAHVSGAV  
LTFMGMSLYMEVQTILSYQMOPKIHGKQVFWIRLLLVICGVSALSMLTCSVLHSGNFGTDL  
EQKLHWNPEDKGYVLHMITTAAEWSMSFSFFGFFLTYYIRDFQKISLRVEANLHGLTLYDTAPC  
PINNERTRLLSRDI

**Important features:**

**Type II transmembrane domain:**

amino acids 13-33

**Other Transmembrane domains:**

amino acids 54-73, 94-113, 160-180, 122-141

**N-myristoylation sites.**

amino acids 57-63, 95-101, 99-105, 124-130, 183-189

(57) Abstract: The present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

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Avenue, San Francisco, CA 94122 (US). GURNEY, Austin, L. [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). WATANABE, Colin, K. [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). WOOD, William, I. [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US).

(74) Agents: KRESNAK, Mark, T. et al.; Genentech, Inc., MS49, 1 DNA Way, South San Francisco, CA 94080-4990 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- Without international search report and to be republished upon receipt of that report.
- With (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

## SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

### FIELD OF THE INVENTION

The present invention relates generally to the identification and isolation of novel DNA and to the  
5 recombinant production of novel polypeptides.

### BACKGROUND OF THE INVENTION

Extracellular proteins play important roles in, among other things, the formation, differentiation and  
maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration,  
10 differentiation, or interaction with other cells, is typically governed by information received from other cells  
and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance,  
mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which  
are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted  
polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of  
15 action in the extracellular environment.

Secreted proteins have various industrial applications, including as pharmaceuticals, diagnostics,  
biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons,  
interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins.  
Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts  
20 are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are  
focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel  
secreted proteins. Examples of screening methods and techniques are described in the literature [see, for  
example, Klein et al., *Proc. Natl. Acad. Sci.* 93:7108-7113 (1996); U.S. Patent No. 5,536,637].

Membrane-bound proteins and receptors can play important roles in, among other things, the formation,  
25 differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation,  
migration, differentiation, or interaction with other cells, is typically governed by information received from  
other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides  
(for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and  
hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins.  
30 Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor  
kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesion molecules like  
selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is  
regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze  
that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and

nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interactions. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

5        Efforts are being undertaken by both industry and academia to identify new, native receptor or membrane-bound proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor or membrane-bound proteins.

#### SUMMARY OF THE INVENTION

10        In one embodiment, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

15        In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

25        In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94%



nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20 nucleotides in length, alternatively at least about 30 nucleotides in length, alternatively at least about 40 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 70 nucleotides in length, alternatively at least about 80 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 110 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 130 nucleotides in length, alternatively at least about 140 nucleotides in length,

alternatively at least about 150 nucleotides in length, alternatively at least about 160 nucleotides in length, alternatively at least about 170 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 190 nucleotides in length, alternatively at least about 200 nucleotides in length, alternatively at least about 250 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 350 nucleotides in length, alternatively at least about 400 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 500 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 700 nucleotides in length, alternatively at least about 800 nucleotides in length, alternatively at least about 900 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83%

amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about 91% amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about 97% amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention concerns a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cell comprising any such vector are also provided. By

way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules  
5 comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which binds, preferably specifically, to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

10 In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

In yet other embodiments, the present invention is directed to methods of using the PRO polypeptides of the present invention for a variety of uses based upon the functional biological assay data presented in the  
15 Examples below.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO180 cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA26843-1389".

20 Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) of a native sequence PRO218 cDNA, wherein SEQ ID NO:3 is a clone designated herein as "DNA30867-1335".

25 Figure 4 shows the amino acid sequence (SEQ ID NO:4) derived from the coding sequence of SEQ ID NO:3 shown in Figure 3.

Figure 5 shows a nucleotide sequence (SEQ ID NO:5) of a native sequence PRO263 cDNA, wherein SEQ ID NO:5 is a clone designated herein as "DNA34431-1177".

Figure 6 shows the amino acid sequence (SEQ ID NO:6) derived from the coding sequence of SEQ ID NO:5 shown in Figure 5.

30 Figure 7 shows a nucleotide sequence (SEQ ID NO:7) of a native sequence PRO295 cDNA, wherein SEQ ID NO:7 is a clone designated herein as "DNA38268-1188".

Figure 8 shows the amino acid sequence (SEQ ID NO:8) derived from the coding sequence of SEQ ID NO:7 shown in Figure 7.

35 Figure 9 shows a nucleotide sequence (SEQ ID NO:9) of a native sequence PRO874 cDNA, wherein SEQ ID NO:9 is a clone designated herein as "DNA40621-1440".

Figure 10 shows the amino acid sequence (SEQ ID NO:10) derived from the coding sequence of SEQ ID NO:9 shown in Figure 9.

Figure 11 shows a nucleotide sequence (SEQ ID NO:11) of a native sequence PRO300 cDNA, wherein SEQ ID NO:11 is a clone designated herein as "DNA40625-1189".

Figure 12 shows the amino acid sequence (SEQ ID NO:12) derived from the coding sequence of SEQ ID NO:11 shown in Figure 11.

Figure 13 shows a nucleotide sequence (SEQ ID NO:13) of a native sequence PRO1864 cDNA, wherein  
5 SEQ ID NO:13 is a clone designated herein as "DNA45409-2511".

Figure 14 shows the amino acid sequence (SEQ ID NO:14) derived from the coding sequence of SEQ ID NO:13 shown in Figure 13.

Figure 15 shows a nucleotide sequence (SEQ ID NO:15) of a native sequence PRO1282 cDNA, wherein  
10 SEQ ID NO:15 is a clone designated herein as "DNA45495-1550".

Figure 16 shows the amino acid sequence (SEQ ID NO:16) derived from the coding sequence of SEQ ID NO:15 shown in Figure 15.

Figure 17 shows a nucleotide sequence (SEQ ID NO:17) of a native sequence PRO1063 cDNA, wherein  
SEQ ID NO:17 is a clone designated herein as "DNA49820-1427".

Figure 18 shows the amino acid sequence (SEQ ID NO:18) derived from the coding sequence of SEQ  
15 ID NO:17 shown in Figure 17.

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) of a native sequence PRO1773 cDNA, wherein  
SEQ ID NO:19 is a clone designated herein as "DNA56406-1704".

Figure 20 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ  
ID NO:19 shown in Figure 19.

Figure 21 shows a nucleotide sequence (SEQ ID NO:21) of a native sequence PRO1013 cDNA, wherein  
20 SEQ ID NO:21 is a clone designated herein as "DNA56410-1414".

Figure 22 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ  
ID NO:21 shown in Figure 21.

Figure 23 shows a nucleotide sequence (SEQ ID NO:23) of a native sequence PRO937 cDNA, wherein  
25 SEQ ID NO:23 is a clone designated herein as "DNA56436-1448".

Figure 24 shows the amino acid sequence (SEQ ID NO:24) derived from the coding sequence of SEQ  
ID NO:23 shown in Figure 23.

Figure 25 shows a nucleotide sequence (SEQ ID NO:25) of a native sequence PRO842 cDNA, wherein  
SEQ ID NO:25 is a clone designated herein as "DNA56855-1447".

Figure 26 shows the amino acid sequence (SEQ ID NO:26) derived from the coding sequence of SEQ  
30 ID NO:25 shown in Figure 25.

Figure 27 shows a nucleotide sequence (SEQ ID NO:27) of a native sequence PRO1180 cDNA, wherein  
SEQ ID NO:27 is a clone designated herein as "DNA56860-1510".

Figure 28 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ  
35 ID NO:27 shown in Figure 27.

Figure 29 shows a nucleotide sequence (SEQ ID NO:29) of a native sequence PRO831 cDNA, wherein  
SEQ ID NO:29 is a clone designated herein as "DNA56862-1343".

Figure 30 shows the amino acid sequence (SEQ ID NO:30) derived from the coding sequence of SEQ ID NO:29 shown in Figure 29.

Figure 31 shows a nucleotide sequence (SEQ ID NO:31) of a native sequence PRO1115 cDNA, wherein SEQ ID NO:31 is a clone designated herein as "DNA56868-1478".

Figure 32 shows the amino acid sequence (SEQ ID NO:32) derived from the coding sequence of SEQ ID NO:31 shown in Figure 31.

Figure 33 shows a nucleotide sequence (SEQ ID NO:33) of a native sequence PRO1277 cDNA, wherein SEQ ID NO:33 is a clone designated herein as "DNA56869-1545".

Figure 34 shows the amino acid sequence (SEQ ID NO:34) derived from the coding sequence of SEQ ID NO:33 shown in Figure 33.

Figure 35 shows a nucleotide sequence (SEQ ID NO:35) of a native sequence PRO1074 cDNA, wherein SEQ ID NO:35 is a clone designated herein as "DNA57704-1452".

Figure 36 shows the amino acid sequence (SEQ ID NO:36) derived from the coding sequence of SEQ ID NO:35 shown in Figure 35.

Figure 37 shows a nucleotide sequence (SEQ ID NO:37) of a native sequence PRO1344 cDNA, wherein SEQ ID NO:37 is a clone designated herein as "DNA58723-1588".

Figure 38 shows the amino acid sequence (SEQ ID NO:38) derived from the coding sequence of SEQ ID NO:37 shown in Figure 37.

Figure 39 shows a nucleotide sequence (SEQ ID NO:39) of a native sequence PRO1136 cDNA, wherein SEQ ID NO:39 is a clone designated herein as "DNA57827-1493".

Figure 40 shows the amino acid sequence (SEQ ID NO:40) derived from the coding sequence of SEQ ID NO:39 shown in Figure 39.

Figure 41 shows a nucleotide sequence (SEQ ID NO:41) of a native sequence PRO1109 cDNA, wherein SEQ ID NO:41 is a clone designated herein as "DNA58737-1473".

Figure 42 shows the amino acid sequence (SEQ ID NO:42) derived from the coding sequence of SEQ ID NO:41 shown in Figure 41.

Figure 43 shows a nucleotide sequence (SEQ ID NO:43) of a native sequence PRO1003 cDNA, wherein SEQ ID NO:43 is a clone designated herein as "DNA58846-1409".

Figure 44 shows the amino acid sequence (SEQ ID NO:44) derived from the coding sequence of SEQ ID NO:43 shown in Figure 43.

Figure 45 shows a nucleotide sequence (SEQ ID NO:45) of a native sequence PRO1138 cDNA, wherein SEQ ID NO:45 is a clone designated herein as "DNA58850-1495".

Figure 46 shows the amino acid sequence (SEQ ID NO:46) derived from the coding sequence of SEQ ID NO:45 shown in Figure 45.

Figure 47 shows a nucleotide sequence (SEQ ID NO:47) of a native sequence PRO994 cDNA, wherein SEQ ID NO:47 is a clone designated herein as "DNA58855-1422".

Figure 48 shows the amino acid sequence (SEQ ID NO:48) derived from the coding sequence of SEQ ID NO:47 shown in Figure 47.

Figure 49 shows a nucleotide sequence (SEQ ID NO:49) of a native sequence PRO1069 cDNA, wherein SEQ ID NO:49 is a clone designated herein as "DNA59211-1450".

Figure 50 shows the amino acid sequence (SEQ ID NO:50) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence PRO1411 cDNA, wherein  
5 SEQ ID NO:51 is a clone designated herein as "DNA59212-1627".

Figure 52 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 51.

Figure 53 shows a nucleotide sequence (SEQ ID NO:53) of a native sequence PRO1129 cDNA, wherein  
10 SEQ ID NO:53 is a clone designated herein as "DNA59213-1487".

Figure 54 shows the amino acid sequence (SEQ ID NO:54) derived from the coding sequence of SEQ ID NO:53 shown in Figure 53.

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) of a native sequence PRO1027 cDNA, wherein  
SEQ ID NO:55 is a clone designated herein as "DNA59605-1418".

Figure 56 shows the amino acid sequence (SEQ ID NO:56) derived from the coding sequence of SEQ  
15 ID NO:55 shown in Figure 55.

Figure 57 shows a nucleotide sequence (SEQ ID NO:57) of a native sequence PRO1106 cDNA, wherein  
SEQ ID NO:57 is a clone designated herein as "DNA59609-1470".

Figure 58 shows the amino acid sequence (SEQ ID NO:58) derived from the coding sequence of SEQ  
ID NO:57 shown in Figure 57.

Figure 59 shows a nucleotide sequence (SEQ ID NO:59) of a native sequence PRO1291 cDNA, wherein  
20 SEQ ID NO:59 is a clone designated herein as "DNA59610-1556".

Figure 60 shows the amino acid sequence (SEQ ID NO:60) derived from the coding sequence of SEQ  
ID NO:59 shown in Figure 59.

Figure 61 shows a nucleotide sequence (SEQ ID NO:61) of a native sequence PRO3573 cDNA, wherein  
25 SEQ ID NO:61 is a clone designated herein as "DNA59837-2545".

Figure 62 shows the amino acid sequence (SEQ ID NO:62) derived from the coding sequence of SEQ  
ID NO:61 shown in Figure 61.

Figure 63 shows a nucleotide sequence (SEQ ID NO:63) of a native sequence PRO3566 cDNA, wherein  
SEQ ID NO:63 is a clone designated herein as "DNA59844-2542".

Figure 64 shows the amino acid sequence (SEQ ID NO:64) derived from the coding sequence of SEQ  
30 ID NO:63 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) of a native sequence PRO1098 cDNA, wherein  
SEQ ID NO:65 is a clone designated herein as "DNA59854-1459".

Figure 66 shows the amino acid sequence (SEQ ID NO:66) derived from the coding sequence of SEQ  
35 ID NO:65 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) of a native sequence PRO1158 cDNA, wherein  
SEQ ID NO:67 is a clone designated herein as "DNA60625-1507".

Figure 68 shows the amino acid sequence (SEQ ID NO:68) derived from the coding sequence of SEQ ID NO:67 shown in Figure 67.

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) of a native sequence PRO1124 cDNA, wherein SEQ ID NO:69 is a clone designated herein as "DNA60629-1481".

5 Figure 70 shows the amino acid sequence (SEQ ID NO:70) derived from the coding sequence of SEQ ID NO:69 shown in Figure 69.

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) of a native sequence PRO1287 cDNA, wherein SEQ ID NO:71 is a clone designated herein as "DNA61755-1554".

Figure 72 shows the amino acid sequence (SEQ ID NO:72) derived from the coding sequence of SEQ ID NO:71 shown in Figure 71.

10 Figure 73 shows a nucleotide sequence (SEQ ID NO:73) of a native sequence PRO1335 cDNA, wherein SEQ ID NO:73 is a clone designated herein as "DNA62812-1594".

Figure 74 shows the amino acid sequence (SEQ ID NO:74) derived from the coding sequence of SEQ ID NO:73 shown in Figure 73.

15 Figure 75 shows a nucleotide sequence (SEQ ID NO:75) of a native sequence PRO1315 cDNA, wherein SEQ ID NO:75 is a clone designated herein as "DNA62815-1576".

Figure 76 shows the amino acid sequence (SEQ ID NO:76) derived from the coding sequence of SEQ ID NO:75 shown in Figure 75.

Figure 77 shows a nucleotide sequence (SEQ ID NO:77) of a native sequence PRO1357 cDNA, wherein SEQ ID NO:77 is a clone designated herein as "DNA64881-1602".

20 Figure 78 shows the amino acid sequence (SEQ ID NO:78) derived from the coding sequence of SEQ ID NO:77 shown in Figure 77.

Figure 79 shows a nucleotide sequence (SEQ ID NO:79) of a native sequence PRO1356 cDNA, wherein SEQ ID NO:79 is a clone designated herein as "DNA64886-1601".

25 Figure 80 shows the amino acid sequence (SEQ ID NO:80) derived from the coding sequence of SEQ ID NO:79 shown in Figure 79.

Figure 81 shows a nucleotide sequence (SEQ ID NO:81) of a native sequence PRO1557 cDNA, wherein SEQ ID NO:81 is a clone designated herein as "DNA64902-1667".

Figure 82 shows the amino acid sequence (SEQ ID NO:82) derived from the coding sequence of SEQ ID NO:81 shown in Figure 81.

30 Figure 83 shows a nucleotide sequence (SEQ ID NO:83) of a native sequence PRO1347 cDNA, wherein SEQ ID NO:83 is a clone designated herein as "DNA64950-1590".

Figure 84 shows the amino acid sequence (SEQ ID NO:84) derived from the coding sequence of SEQ ID NO:83 shown in Figure 83.

35 Figure 85 shows a nucleotide sequence (SEQ ID NO:85) of a native sequence PRO1302 cDNA, wherein SEQ ID NO:85 is a clone designated herein as "DNA65403-1565".

Figure 86 shows the amino acid sequence (SEQ ID NO:86) derived from the coding sequence of SEQ ID NO:85 shown in Figure 85.



Figure 87 shows a nucleotide sequence (SEQ ID NO:87) of a native sequence PRO1270 cDNA, wherein SEQ ID NO:87 is a clone designated herein as "DNA66308-1537".

Figure 88 shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:87 shown in Figure 87.

Figure 89 shows a nucleotide sequence (SEQ ID NO:89) of a native sequence PRO1268 cDNA, wherein  
5 SEQ ID NO:89 is a clone designated herein as "DNA66519-1535".

Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 89.

Figure 91 shows a nucleotide sequence (SEQ ID NO:91) of a native sequence PRO1327 cDNA, wherein  
10 SEQ ID NO:91 is a clone designated herein as "DNA66521-1583".

Figure 92 shows the amino acid sequence (SEQ ID NO:92) derived from the coding sequence of SEQ ID NO:91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) of a native sequence PRO1328 cDNA, wherein  
15 SEQ ID NO:93 is a clone designated herein as "DNA66658-1584".

Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ ID NO:93 shown in Figure 93.

Figure 95 shows a nucleotide sequence (SEQ ID NO:95) of a native sequence PRO1329 cDNA, wherein  
20 SEQ ID NO:95 is a clone designated herein as "DNA66660-1585".

Figure 96 shows the amino acid sequence (SEQ ID NO:96) derived from the coding sequence of SEQ ID NO:95 shown in Figure 95.

Figure 97 shows a nucleotide sequence (SEQ ID NO:97) of a native sequence PRO1340 cDNA, wherein  
25 SEQ ID NO:97 is a clone designated herein as "DNA66663-1598".

Figure 98 shows the amino acid sequence (SEQ ID NO:98) derived from the coding sequence of SEQ ID NO:97 shown in Figure 97.

Figure 99 shows a nucleotide sequence (SEQ ID NO:99) of a native sequence PRO1342 cDNA, wherein  
30 SEQ ID NO:99 is a clone designated herein as "DNA66674-1599".

Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:99 shown in Figure 99.

Figure 101 shows a nucleotide sequence (SEQ ID NO:101) of a native sequence PRO3579 cDNA, wherein  
35 SEQ ID NO:101 is a clone designated herein as "DNA68862-2546".

Figure 102 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:101 shown in Figure 101.

Figure 103 shows a nucleotide sequence (SEQ ID NO:103) of a native sequence PRO1472 cDNA, wherein  
40 SEQ ID NO:103 is a clone designated herein as "DNA68866-1644".

Figure 104 shows the amino acid sequence (SEQ ID NO:104) derived from the coding sequence of SEQ ID NO:103 shown in Figure 103.

Figure 105 shows a nucleotide sequence (SEQ ID NO:105) of a native sequence PRO1461 cDNA, wherein  
45 SEQ ID NO:105 is a clone designated herein as "DNA68871-1638".

Figure 106 shows the amino acid sequence (SEQ ID NO:106) derived from the coding sequence of SEQ ID NO:105 shown in Figure 105.

Figure 107 shows a nucleotide sequence (SEQ ID NO:107) of a native sequence PRO1568 cDNA, wherein SEQ ID NO:107 is a clone designated herein as "DNA68880-1676".

5 Figure 108 shows the amino acid sequence (SEQ ID NO:108) derived from the coding sequence of SEQ ID NO:107 shown in Figure 107.

Figure 109 shows a nucleotide sequence (SEQ ID NO:109) of a native sequence PRO1753 cDNA, wherein SEQ ID NO:109 is a clone designated herein as "DNA68883-1691".

Figure 110 shows the amino acid sequence (SEQ ID NO:110) derived from the coding sequence of SEQ ID NO:109 shown in Figure 109.

10 Figure 111 shows a nucleotide sequence (SEQ ID NO:111) of a native sequence PRO1570 cDNA, wherein SEQ ID NO:111 is a clone designated herein as "DNA68885-1678".

Figure 112 shows the amino acid sequence (SEQ ID NO:112) derived from the coding sequence of SEQ ID NO:111 shown in Figure 111.

15 Figure 113 shows a nucleotide sequence (SEQ ID NO:113) of a native sequence PRO1446 cDNA, wherein SEQ ID NO:113 is a clone designated herein as "DNA71277-1636".

Figure 114 shows the amino acid sequence (SEQ ID NO:114) derived from the coding sequence of SEQ ID NO:113 shown in Figure 113.

Figure 115 shows a nucleotide sequence (SEQ ID NO:115) of a native sequence PRO1565 cDNA, wherein SEQ ID NO:115 is a clone designated herein as "DNA73727-1673".

20 Figure 116 shows the amino acid sequence (SEQ ID NO:116) derived from the coding sequence of SEQ ID NO:115 shown in Figure 115.

Figure 117 shows a nucleotide sequence (SEQ ID NO:117) of a native sequence PRO1572 cDNA, wherein SEQ ID NO:117 is a clone designated herein as "DNA73734-1680".

25 Figure 118 shows the amino acid sequence (SEQ ID NO:118) derived from the coding sequence of SEQ ID NO:117 shown in Figure 117.

Figure 119 shows a nucleotide sequence (SEQ ID NO:119) of a native sequence PRO1573 cDNA, wherein SEQ ID NO:119 is a clone designated herein as "DNA73735-1681".

Figure 120 shows the amino acid sequence (SEQ ID NO:120) derived from the coding sequence of SEQ ID NO:119 shown in Figure 119.

30 Figure 121 shows a nucleotide sequence (SEQ ID NO:121) of a native sequence PRO1550 cDNA, wherein SEQ ID NO:121 is a clone designated herein as "DNA76393-1664".

Figure 122 shows the amino acid sequence (SEQ ID NO:122) derived from the coding sequence of SEQ ID NO:121 shown in Figure 121.

35 Figure 123 shows a nucleotide sequence (SEQ ID NO:123) of a native sequence PRO1693 cDNA, wherein SEQ ID NO:123 is a clone designated herein as "DNA77301-1708".

Figure 124 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:123 shown in Figure 123.

Figure 125 shows a nucleotide sequence (SEQ ID NO:125) of a native sequence PRO1566 cDNA, wherein SEQ ID NO:125 is a clone designated herein as "DNA77568-1626".

Figure 126 shows the amino acid sequence (SEQ ID NO:126) derived from the coding sequence of SEQ ID NO:125 shown in Figure 125.

5 Figure 127 shows a nucleotide sequence (SEQ ID NO:127) of a native sequence PRO1774 cDNA, wherein SEQ ID NO:127 is a clone designated herein as "DNA77626-1705".

Figure 128 shows the amino acid sequence (SEQ ID NO:128) derived from the coding sequence of SEQ ID NO:127 shown in Figure 127.

Figure 129 shows a nucleotide sequence (SEQ ID NO:129) of a native sequence PRO1928 cDNA, wherein SEQ ID NO:129 is a clone designated herein as "DNA81754-2532".

10 Figure 130 shows the amino acid sequence (SEQ ID NO:130) derived from the coding sequence of SEQ ID NO:129 shown in Figure 129.

Figure 131 shows a nucleotide sequence (SEQ ID NO:131) of a native sequence PRO1865 cDNA, wherein SEQ ID NO:131 is a clone designated herein as "DNA81757-2512".

15 Figure 132 shows the amino acid sequence (SEQ ID NO:132) derived from the coding sequence of SEQ ID NO:131 shown in Figure 131.

Figure 133 shows a nucleotide sequence (SEQ ID NO:133) of a native sequence PRO1925 cDNA, wherein SEQ ID NO:133 is a clone designated herein as "DNA82302-2529".

Figure 134 shows the amino acid sequence (SEQ ID NO:134) derived from the coding sequence of SEQ ID NO:133 shown in Figure 133.

20 Figure 135 shows a nucleotide sequence (SEQ ID NO:135) of a native sequence PRO1926 cDNA, wherein SEQ ID NO:135 is a clone designated herein as "DNA82340-2530".

Figure 136 shows the amino acid sequence (SEQ ID NO:136) derived from the coding sequence of SEQ ID NO:135 shown in Figure 135.

25 Figure 137 shows a nucleotide sequence (SEQ ID NO:137) of a native sequence PRO1801 cDNA, wherein SEQ ID NO:137 is a clone designated herein as "DNA83500-2506".

Figure 138 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:137 shown in Figure 137.

Figure 139 shows a nucleotide sequence (SEQ ID NO:139) of a native sequence PRO4405 cDNA, wherein SEQ ID NO:139 is a clone designated herein as "DNA84920-2614".

30 Figure 140 shows the amino acid sequence (SEQ ID NO:140) derived from the coding sequence of SEQ ID NO:139 shown in Figure 139.

Figure 141 shows a nucleotide sequence (SEQ ID NO:141) of a native sequence PRO3435 cDNA, wherein SEQ ID NO:141 is a clone designated herein as "DNA85066-2534".

35 Figure 142 shows the amino acid sequence (SEQ ID NO:142) derived from the coding sequence of SEQ ID NO:141 shown in Figure 141.

Figure 143 shows a nucleotide sequence (SEQ ID NO:143) of a native sequence PRO3543 cDNA, wherein SEQ ID NO:143 is a clone designated herein as "DNA86571-2551".

Figure 144 shows the amino acid sequence (SEQ ID NO:144) derived from the coding sequence of SEQ ID NO:143 shown in Figure 143.

Figure 145 shows a nucleotide sequence (SEQ ID NO:145) of a native sequence PRO3443 cDNA, wherein SEQ ID NO:145 is a clone designated herein as "DNA87991-2540".

5 Figure 146 shows the amino acid sequence (SEQ ID NO:146) derived from the coding sequence of SEQ ID NO:145 shown in Figure 145.

Figure 147 shows a nucleotide sequence (SEQ ID NO:147) of a native sequence PRO3442 cDNA, wherein SEQ ID NO:147 is a clone designated herein as "DNA92238-2539".

Figure 148 shows the amino acid sequence (SEQ ID NO:148) derived from the coding sequence of SEQ ID NO:147 shown in Figure 147.

10 Figure 149 shows a nucleotide sequence (SEQ ID NO:149) of a native sequence PRO5990 cDNA, wherein SEQ ID NO:149 is a clone designated herein as "DNA96042-2682".

Figure 150 shows the amino acid sequence (SEQ ID NO:150) derived from the coding sequence of SEQ ID NO:149 shown in Figure 149.

15 Figure 151 shows a nucleotide sequence (SEQ ID NO:151) of a native sequence PRO4342 cDNA, wherein SEQ ID NO:151 is a clone designated herein as "DNA96787-2534".

Figure 152 shows the amino acid sequence (SEQ ID NO:152) derived from the coding sequence of SEQ ID NO:151 shown in Figure 151.

Figure 153 shows a nucleotide sequence (SEQ ID NO:153) of a native sequence PRO10096 cDNA, wherein SEQ ID NO:153 is a clone designated herein as "DNA125185-2806".

20 Figure 154 shows the amino acid sequence (SEQ ID NO:154) derived from the coding sequence of SEQ ID NO:153 shown in Figure 153.

Figure 155 shows a nucleotide sequence (SEQ ID NO:155) of a native sequence PRO10272 cDNA, wherein SEQ ID NO:155 is a clone designated herein as "DNA147531-2821".

25 Figure 156 shows the amino acid sequence (SEQ ID NO:156) derived from the coding sequence of SEQ ID NO:155 shown in Figure 155.

Figure 157 shows a nucleotide sequence (SEQ ID NO:157) of a native sequence PRO5801 cDNA, wherein SEQ ID NO:157 is a clone designated herein as "DNA115291-2681".

Figure 158 shows the amino acid sequence (SEQ ID NO:158) derived from the coding sequence of SEQ ID NO:157 shown in Figure 157.

30 Figure 159 shows a nucleotide sequence (SEQ ID NO:159) of a native sequence PRO20110 cDNA, wherein SEQ ID NO:159 is a clone designated herein as "DNA166819".

Figure 160 shows the amino acid sequence (SEQ ID NO:160) derived from the coding sequence of SEQ ID NO:159 shown in Figure 159.

35 Figure 161 shows a nucleotide sequence (SEQ ID NO:161) of a native sequence PRO20040 cDNA, wherein SEQ ID NO:161 is a clone designated herein as "DNA164625-2890".

Figure 162 shows the amino acid sequence (SEQ ID NO:162) derived from the coding sequence of SEQ ID NO:161 shown in Figure 161.

Figure 163 shows a nucleotide sequence (SEQ ID NO:163) of a native sequence PRO20233 cDNA, wherein SEQ ID NO:163 is a clone designated herein as "DNA165608".

Figure 164 shows the amino acid sequence (SEQ ID NO:164) derived from the coding sequence of SEQ ID NO:163 shown in Figure 163.

Figure 165 shows a nucleotide sequence (SEQ ID NO:165) of a native sequence PRO19670 cDNA, wherein SEQ ID NO:165 is a clone designated herein as "DNA131639-2874".

Figure 166 shows the amino acid sequence (SEQ ID NO:166) derived from the coding sequence of SEQ ID NO:165 shown in Figure 165.

Figure 167 shows a nucleotide sequence (SEQ ID NO:167) of a native sequence PRO1890 cDNA, wherein SEQ ID NO:167 is a clone designated herein as "DNA79230-2525".

Figure 168 shows the amino acid sequence (SEQ ID NO:168) derived from the coding sequence of SEQ ID NO:167 shown in Figure 167.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

##### I. Definitions

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "PRO polypeptide" refers to each individual PRO/number polypeptide disclosed herein. All disclosures in this specification which refer to the "PRO polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "PRO polypeptide" also includes variants of the PRO/number polypeptides disclosed herein.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino

acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1 % of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5 % of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83% amino acid sequence identity, alternatively at least about 84% amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about 90% amino acid

sequence identity, alternatively at least about 91 % amino acid sequence identity, alternatively at least about 92 % amino acid sequence identity, alternatively at least about 93 % amino acid sequence identity, alternatively at least about 94 % amino acid sequence identity, alternatively at least about 95 % amino acid sequence identity, alternatively at least about 96 % amino acid sequence identity, alternatively at least about 97 % amino acid sequence identity, alternatively at least about 98 % amino acid sequence identity and alternatively at least about 99 % amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20 amino acids in length, alternatively at least about 30 amino acids in length, alternatively at least about 40 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 60 amino acids in length, alternatively at least about 70 amino acids in length, alternatively at least about 80 amino acids in length, alternatively at least about 90 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 150 amino acids in length, alternatively at least about 200 amino acids in length, alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction  $X/Y$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO", wherein "PRO" represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, and "X", "Y" and "Z" each represent different hypothetical amino acid residues.

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % amino acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (i.e., the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an the amino acid sequence A which has or having at least 80% amino acid sequence identity to the amino acid sequence B", the amino acid sequence A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:



100 times the fraction  $X/Y$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81% nucleic acid sequence identity, alternatively at least about 82% nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 210 nucleotides in length, alternatively at least about 240 nucleotides in length, alternatively at least about 270 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to PRO-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA", wherein "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides.

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % nucleic acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and

scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (i.e., the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from <http://www.ncbi.nlm.nih.gov> or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous

solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" PRO polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide-encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-PRO monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO antibody compositions with polypeptopic specificity, single chain anti-PRO antibodies, and fragments of anti-PRO antibodies (see below). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when

complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any

immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native PRO polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native PRO polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a PRO polypeptide may comprise contacting a PRO polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO polypeptide.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-

forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')<sub>2</sub>, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')<sub>2</sub> fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V<sub>H</sub>-V<sub>L</sub> dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')<sub>2</sub> antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

"Single-chain Fv" or "sFv" antibody fragments comprise the V<sub>H</sub> and V<sub>L</sub> domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V<sub>H</sub> and V<sub>L</sub> domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V<sub>H</sub>) connected to a light-chain variable domain (V<sub>L</sub>) in the same polypeptide chain (V<sub>H</sub>-V<sub>L</sub>). By using a linker that is too short to allow pairing between the two domains

on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

5 An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or  
10 nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

15 An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

20 By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes  
25 a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a PRO polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

30 A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.



Table 1

```

/*
 *
 * C-C increased from 12 to 15
 * Z is average of EQ
5  * B is average of ND
 * match with stop is _M; stop-stop = 0; J (joker) match = 0
 */
#define _M      -8      /* value of a match with a stop */

10 int  _day[26][26] = {
/*  A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
/* A */ { 2, 0, -2, 0, 0, -4, 1, -1, -1, 0, -1, -2, -1, 0, _M, 1, 0, -2, 1, 1, 0, 0, -6, 0, -3, 0},
/* B */ { 0, 3, -4, 3, 2, -5, 0, 1, -2, 0, 0, -3, -2, 2, _M, -1, 1, 0, 0, 0, 0, -2, -5, 0, -3, 1},
/* C */ {-2, -4, 15, -5, -5, -4, -3, -2, 0, -5, -6, -5, -4, _M, -3, -5, -4, 0, -2, 0, -2, -8, 0, 0, -5},
15 /* D */ { 0, 3, -5, 4, 3, -6, 1, 1, -2, 0, 0, -4, -3, 2, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 2},
/* E */ { 0, 2, -5, 3, 4, -5, 0, 1, -2, 0, 0, -3, -2, 1, _M, -1, 2, -1, 0, 0, 0, -2, -7, 0, -4, 3},
/* F */ {-4, -5, -4, -6, -5, 9, -5, -2, 1, 0, -5, 2, 0, -4, _M, -5, -5, -4, -3, -3, 0, -1, 0, 0, 7, -5},
/* G */ { 1, 0, -3, 1, 0, -5, 5, -2, -3, 0, -2, -4, -3, 0, _M, -1, -1, -3, 1, 0, 0, -1, -7, 0, -5, 0},
/* H */ {-1, 1, -3, 1, 1, -2, -2, 6, -2, 0, 0, -2, -2, 2, _M, 0, 3, 2, -1, -1, 0, -2, -3, 0, 0, 2},
20 /* I */ {-1, -2, -2, -2, -2, 1, -3, -2, 5, 0, -2, 2, 2, -2, _M, -2, -2, -2, -1, 0, 0, 4, -5, 0, -1, -2},
/* J */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */ {-1, 0, -5, 0, 0, -5, -2, 0, -2, 0, 5, -3, 0, 1, _M, -1, 1, 3, 0, 0, 0, -2, -3, 0, -4, 0},
/* L */ {-2, -3, -6, -4, -3, 2, -4, -2, 2, 0, -3, 6, 4, -3, _M, -3, -2, -3, -3, -1, 0, 2, -2, 0, -1, -2},
/* M */ {-1, -2, -5, -3, -2, 0, -3, -2, 2, 0, 0, 4, 6, -2, _M, -2, -1, 0, -2, -1, 0, 2, -4, 0, -2, -1},
25 /* N */ { 0, 2, -4, 2, 1, -4, 0, 2, -2, 0, 1, -3, -2, 2, _M, -1, 1, 0, 1, 0, 0, -2, -4, 0, -2, 1},
/* O */ { _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, _M, 0, _M, _M, _M, _M, _M, _M, _M, _M, _M},
/* P */ { 1, -1, -3, -1, -1, -5, -1, 0, -2, 0, -1, -3, -2, -1, _M, 6, 0, 0, 1, 0, 0, -1, -6, 0, -5, 0},
/* Q */ { 0, 1, -5, 2, 2, -5, -1, 3, -2, 0, 1, -2, -1, 1, _M, 0, 4, 1, -1, -1, 0, -2, -5, 0, -4, 3},
/* R */ {-2, 0, -4, -1, -1, -4, -3, 2, -2, 0, 3, -3, 0, 0, _M, 0, 1, 6, 0, -1, 0, -2, 2, 0, -4, 0},
30 /* S */ { 1, 0, 0, 0, 0, -3, 1, -1, -1, 0, 0, -3, -2, 1, _M, 1, -1, 0, 2, 1, 0, -1, -2, 0, -3, 0},
/* T */ { 1, 0, -2, 0, 0, -3, 0, -1, 0, 0, 0, -1, -1, 0, _M, 0, -1, -1, 1, 3, 0, 0, -5, 0, -3, 0},
/* U */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */ { 0, -2, -2, -2, -2, -1, -1, -2, 4, 0, -2, 2, 2, -2, _M, -1, -2, -2, -1, 0, 0, 4, -6, 0, -2, -2},
35 /* W */ {-6, -5, -8, -7, -7, 0, -7, -3, -5, 0, -3, -2, -4, -4, _M, -6, -5, 2, -2, -5, 0, -6, 17, 0, 0, -6},
/* X */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, _M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */ {-3, -3, 0, -4, -4, 7, -5, 0, -1, 0, -4, -1, -2, -2, _M, -5, -4, -4, -3, -3, 0, -2, 0, 0, 10, -4},
/* Z */ { 0, 1, -5, 2, 3, -5, 0, 2, -2, 0, 0, -2, -1, 1, _M, 0, 3, 0, 0, 0, 0, -2, -6, 0, -4, 4}
};

```

Table 1 (cont')

```

/*
*/
#include <stdio.h>
#include <ctype.h>

5
#define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define JMPS        1024    /* max jmps in an path */
10
#define MX          4      /* save if there's at least MX-1 bases since last jmp */

#define DMAT        3      /* value of matching bases */
#define DMIS        0      /* penalty for mismatched bases */
#define DINS0       8      /* penalty for a gap */
15
#define DINS1       1      /* penalty per base */
#define PINS0       8      /* penalty for a gap */
#define PINS1       4      /* penalty per residue */

struct jmp {
20
    short            n[MAXJMP]; /* size of jmp (neg for dely) */
    unsigned short   x[MAXJMP]; /* base no. of jmp in seq x */
}; /* limits seq to 2^16-1 */

struct diag {
25
    int              score;      /* score at last jmp */
    long             offset;     /* offset of prev block */
    short            jmp;        /* current jmp index */
    struct jmp        jp;        /* list of jmps */
};

30
struct path {
    int              spc;        /* number of leading spaces */
    short            n[JMPS]; /* size of jmp (gap) */
    int              x[JMPS]; /* loc of jmp (last elem before gap) */
35
};

char              *ofile;      /* output file name */
char              *namex[2];   /* seq names: getseqs() */
char              *prog;       /* prog name for err msgs */
40
char              *seqx[2];     /* seqs: getseqs() */
int               dmax;        /* best diag: nw() */
int               dmax0;       /* final diag */
int               dna;         /* set if dna: main() */
int               endgaps;     /* set if penalizing end gaps */
45
int               gapx, gapy;   /* total gaps in seqs */
int               len0, len1;   /* seq lens */
int               ngapx, ngapy; /* total size of gaps */
int               smax;        /* max score: nw() */
int               *xbm;        /* bitmap for matching */
50
long              offset;      /* current offset in jmp file */
struct            diag         *dx; /* holds diagonals */
struct            path         pp[2]; /* holds path for seqs */

char              *calloc(), *malloc(), *index(), *strcpy();
55
char              *getseq(), *g_calloc();

```

60

Table 1 (cont')

```

/* Needleman-Wunsch alignment program
*
* usage: progs file1 file2
* where file1 and file2 are two dna or two protein sequences.
5  * The sequences can be in upper- or lower-case and may contain ambiguity
* Any lines beginning with ';', '>' or '<' are ignored
* Max file length is 65535 (limited by unsigned short x in the jmp struct)
* A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
10 * Output is in the file "align.out"
*
* The program may create a tmp file in /tmp to hold info about traceback.
* Original version developed under BSD 4.3 on a vax 8650
*/
15 #include "nw.h"
#include "day.h"

static _dbval[26] = {
    1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

20 static _pbval[26] = {
    1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
    128, 256, 0xFFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
    1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
25 1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)                                main
30     int    ac;
    char    *av[ ];
{
    prog = av[0];
    if (ac != 3) {
35         fprintf(stderr, "usage: %s file1 file2\n", prog);
        fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr, "The sequences can be in upper- or lower-case\n");
        fprintf(stderr, "Any lines beginning with ';' or '<' are ignored\n");
        fprintf(stderr, "Output is in the file \"align.out\"\n");
        exit(1);
40     }
    namex[0] = av[1];
    namex[1] = av[2];
    seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
45     xbm = (dna)? _dbval : _pbval;

    endgaps = 0;                                /* 1 to penalize endgaps */
    ofile = "align.out";                        /* output file */

50     nw();                                    /* fill in the matrix, get the possible jmps */
    readjumps();                                /* get the actual jmps */
    print();                                    /* print stats, alignment */

55     cleanup(0);                            /* unlink any tmp files */
}

```

Table 1 (cont')

/\* do the alignment, return best score: main()

\* dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983

\* pro: PAM 250 values

\* When scores are equal, we prefer mismatches to any gap, prefer

\* a new gap to extending an ongoing gap, and prefer a gap in seqx

\* to a gap in seq y.

\*/

nw()

nw

{

```

char      *px, *py;           /* seqs and ptrs */
int        *ndely, *dely;      /* keep track of dely */
int        ndelx, delx;        /* keep track of delx */
int        *tmp;              /* for swapping row0, row1 */
int        mis;               /* score for each type */
int        ins0, ins1;        /* insertion penalties */
register    id;               /* diagonal index */
register    ij;               /* jmp index */
register    *col0, *col1;      /* score for curr, last row */
register    xx, yy;           /* index into seqs */

```

```

dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

```

```

ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));

```

```

dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));

```

```

col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));

```

```

col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));

```

```

ins0 = (dna)? DINS0 : PINS0;

```

```

ins1 = (dna)? DINS1 : PINS1;

```

```

smax = -10000;

```

```

if (endgaps) {

```

```

    for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {

```

```

        col0[yy] = dely[yy] = col0[yy-1] - ins1;

```

```

        ndely[yy] = yy;

```

```

    }

```

```

    col0[0] = 0;      /* Waterman Bull Math Biol 84 */

```

```

}

```

```

else

```

```

    for (yy = 1; yy <= len1; yy++)

```

```

        dely[yy] = -ins0;

```

```

/* fill in match matrix

```

```

*/

```

```

for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {

```

```

    /* initialize first entry in col

```

```

    */

```

```

    if (endgaps) {

```

```

        if (xx == 1)

```

```

            col1[0] = delx = -(ins0+ins1);

```

```

        else

```

```

            col1[0] = delx = col0[0] - ins1;

```

```

        ndelx = xx;

```

```

    }

```

```

    else {

```

```

        col1[0] = 0;

```

```

        delx = -ins0;

```

```

        ndelx = 0;

```

```

    }

```

Table 1 (cont')

...nw

```

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

    /* update penalty for del in x seq;
     * favor new del over ongoing del
     * ignore MAXGAP if weighting endgaps
     */
    if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }

    /* update penalty for del in y seq;
     * favor new del over ongoing del
     */
    if (endgaps || ndelx < MAXGAP) {
        if (col1[yy-1] - ins0 >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
        }
    } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else
            ndelx++;
    }

    /* pick the maximum score; we're favoring
     * mis over any del and delx over dely
     */

```

Table 1 (cont')

...nw

```

id = xx - yy + len1 - 1;
if (mis >= delx && mis >= dely[yy])
    coll[yy] = mis;
5   else if (delx >= dely[yy]) {
    coll[yy] = delx;
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
10   && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
            writejmps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
    }
    dx[id].jp.n[ij] = ndelx;
    dx[id].jp.x[ij] = xx;
    dx[id].score = delx;
    }
    else {
        coll[yy] = dely[yy];
        ij = dx[id].ijmp;
25   if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
            dx[id].ijmp++;
            if (++ij >= MAXJMP) {
                writejmps(id);
                ij = dx[id].ijmp = 0;
                dx[id].offset = offset;
                offset += sizeof(struct jmp) + sizeof(offset);
            }
        }
        dx[id].jp.n[ij] = -ndely[yy];
        dx[id].jp.x[ij] = xx;
        dx[id].score = dely[yy];
    }
    if (xx == len0 && yy < len1) {
40   /* last col
        */
        if (endgaps)
            coll[yy] -= ins0+ins1*(len1-yy);
        if (coll[yy] > smax) {
            smax = coll[yy];
            dmax = id;
        }
    }
    }
50   if (endgaps && xx < len0)
        coll[yy-1] -= ins0+ins1*(len0-xx);
    if (coll[yy-1] > smax) {
        smax = coll[yy-1];
        dmax = id;
    }
55   }
    tmp = col0; col0 = coll; coll = tmp;
}
(void) free((char *)ndely);
(void) free((char *)dely);
60   (void) free((char *)col0);
    (void) free((char *)coll);
    }

```

Table 1 (cont')

```

/*
 *
 * print() -- only routine visible outside this module
 *
5  * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align() -- print alignment of described in array p[ ]: print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
10 * nums() -- put out a number line: dumpblock()
 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() -- put a line of stars: dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */

15 #include "nw.h"

#define SPC      3
#define P_LINE  256 /* maximum output line */
#define P_SPC    3 /* space between name or num and seq */

20 extern _day[26][26];
int olen; /* set output line length */
FILE *fx; /* output file */

25 print()
{
    int lx, ly, firstgap, lastgap; /* overlap */

    if ((fx = fopen(ofile, "w")) == 0) {
30         fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
    fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
35     olen = 60;
    lx = len0;
    ly = len1;
    firstgap = lastgap = 0;
    if (dmax < len1 - 1) { /* leading gap in x */
40         pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
    else if (dmax > len1 - 1) { /* leading gap in y */
45         pp[1].spc = firstgap = dmax - (len1 - 1);
        lx -= pp[1].spc;
    }
    if (dmax0 < len0 - 1) { /* trailing gap in x */
50         lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
    }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
55         lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
    }
    getmat(lx, ly, firstgap, lastgap);
    pr_align();
}

60

```

print

Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
static
5 getmat(lx, ly, firstgap, lastgap)
    int    lx, ly;
    int    firstgap, lastgap;
    /* "core" (minus endgaps) */
    /* leading trailing overlap */

{
10     int    nm, i0, i1, siz0, siz1;
    char    outx[32];
    double   pct;
    register n0, n1;
    register char *p0, *p1;

15     /* get total matches, score
    */
    i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
    p1 = seqx[1] + pp[0].spc;
20     n0 = pp[1].spc + 1;
    n1 = pp[0].spc + 1;

    nm = 0;
    while ( *p0 && *p1 ) {
25         if (siz0) {
            p1++;
            n1++;
            siz0--;
        }
        else if (siz1) {
30             p0++;
            n0++;
            siz1--;
        }
        else {
35             if (xbm[*p0-'A']&xbm[*p1-'A'])
                nm++;
            if (n0++ == pp[0].x[i0])
                siz0 = pp[0].n[i0++];
40             if (n1++ == pp[1].x[i1])
                siz1 = pp[1].n[i1++];
            p0++;
            p1++;
        }
45     }

    /* pct homology:
    * if penalizing endgaps, base is the shorter seq
    * else, knock off overhangs and take shorter core
    */
50     if (endgaps)
        lx = (len0 < len1)? len0 : len1;
    else
        lx = (lx < ly)? lx : ly;
55     pct = 100.*((double)nm)/((double)lx);
    fprintf(fx, "\n");
    fprintf(fx, "< %d match%s in an overlap of %d: %.2f percent similarity\n",
        nm, (nm == 1)? "" : "es", lx, pct);
60

```

getmat



**Table 1 (cont')**

```

fprintf(fx, "<gaps in first sequence: %d", gapx);
if (gapx) {
    (void) sprintf(outx, " (%d %s%s)",
        ngapx, (dna)? "base":"residue", (ngapx == 1)? "" : "s");
    fprintf(fx, "%s", outx);

    fprintf(fx, ", gaps in second sequence: %d", gapy);
    if (gapy) {
        (void) sprintf(outx, " (%d %s%s)",
            ngapy, (dna)? "base":"residue", (ngapy == 1)? "" : "s");
        fprintf(fx, "%s", outx);
    }
    if (dna)
        fprintf(fx,
            "\n< score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
            smax, DMAT, DMIS, DINS0, DINS1);
    else
        fprintf(fx,
            "\n< score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
            smax, PINS0, PINS1);
    if (endgaps)
        fprintf(fx,
            "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
            firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
            lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
    else
        fprintf(fx, "<endgaps not penalized\n");
}

static      nm;          /* matches in core -- for checking */
static      lmax;        /* lengths of stripped file names */
static      ij[2];       /* jmp index for a path */
static      nc[2];       /* number at start of current line */
static      ni[2];       /* current elem number -- for gapping */
static      siz[2];
static char *ps[2];      /* ptr to current element */
static char *po[2];      /* ptr to next output char slot */
static char out[2][P_LINE]; /* output line */
static char star[P_LINE]; /* set by stars() */

/*
 * print alignment of described in struct path pp [ ]
 */
static
pr_align()
{
    int      nn;          /* char count */
    int      more;
    register i;

    for (i = 0, lmax = 0; i < 2; i++) {
        nn = stripname(name[i]);
        if (nn > lmax)
            lmax = nn;

        nc[i] = 1;
        ni[i] = 1;
        siz[i] = ij[i] = 0;
        ps[i] = seqx[i];
        po[i] = out[i];
    }
}

```

...getmat

pr\_align

Table 1 (cont')

...pr\_align

```

for (nn = nm = 0, more = 1; more; ) {
    for (i = more = 0; i < 2; i++) {
        /*
5         * do we have more of this sequence?
        */
        if (!*ps[i])
            continue;

10        more++;

        if (pp[i].spc) { /* leading space */
            *po[i]++ = ' ';
            pp[i].spc--;
15        }
        else if (siz[i]) { /* in a gap */
            *po[i]++ = '-';
            siz[i]--;
20        }
        else { /* we're putting a seq element
            */
            *po[i] = *ps[i];
            if (islower(*ps[i]))
                *ps[i] = toupper(*ps[i]);
25            po[i]++;
            ps[i]++;

            /*
            * are we at next gap for this seq?
            */
            if (ni[i] == pp[i].x[ij[i]]) {
                /*
                * we need to merge all gaps
                * at this location
                */
35                siz[i] = pp[i].n[ij[i]++];
                while (ni[i] == pp[i].x[ij[i]])
                    siz[i] += pp[i].n[ij[i]++];
            }
            ni[i]++;
40        }
    }
    if (++nn == olen || !more && nn) {
        dumpblock();
        for (i = 0; i < 2; i++)
            po[i] = out[i];
        nn = 0;
45    }
}

50 }

/*
 * dump a block of lines, including numbers, stars: pr_align()
 */
55 static
dumpblock()
{
    register i;

60    for (i = 0; i < 2; i++)
        *po[i]-- = '\0';

```

dumpblock

Table 1 (cont')

...dumpblock

```

5      (void) putc('\n', fx);
      for (i = 0; i < 2; i++) {
          if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
              if (i == 0)
                  nums(i);
              if (i == 0 && *out[1])
                  stars();
10         putline(i);
              if (i == 0 && *out[1])
                  fprintf(fx, star);
              if (i == 1)
                  nums(i);
15     }
    }
}

/*
20  * put out a number line: dumpblock()
  */
static
nums(ix)                                nums
25  {
    int    ix;        /* index in out[] holding seq line */

    char    nline[P_LINE];
    register i, j;
    register char    *pn, *px, *py;

30    for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
        *pn = ' ';
    for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
        if (*py == ' ' || *py == '-')
            *pn = ' ';
35        else {
            if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                j = (i < 0)? -i : i;
                for (px = pn; j; j /= 10, px--)
                    *px = j%10 + '0';
40                if (i < 0)
                    *px = '-';
            }
            else
                *pn = ' ';
45            i++;
        }
    }
    *pn = '\0';
    nc[ix] = i;
50    for (pn = nline; *pn; pn++)
        (void) putc(*pn, fx);
    (void) putc('\n', fx);
}

55  /*
  * put out a line (name, [num], seq, [num]): dumpblock()
  */
static
putline(ix)                            putline
60  {
    int    ix;

```

Table 1 (cont')

...putline

```

5      int          i;
      register char *px;

      for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
          (void)putc(*px, fx);
      for (; i < lmax+P_SPC; i++)
          (void)putc(' ', fx);

10     /* these count from 1:
       * ni[] is current element (from 1)
       * nc[] is number at start of current line
       */
      for (px = out[ix]; *px; px++)
          (void)putc(*px&0x7F, fx);
      (void)putc('\n', fx);
  }

20  /*
   * put a line of stars (seqs always in out[0], out[1]): dumpblock()
   */
  static
25  stars()
  {
      int          i;
      register char *p0, *p1, cx, *px;

30     if (!*out[0] || (*out[0] == ' ' && *(p0[0]) == ' ') ||
        !*out[1] || (*out[1] == ' ' && *(p0[1]) == ' '))
        return;
      px = star;
      for (i = lmax+P_SPC; i; i--)
35         *px++ = ' ';

      for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
          if (isalpha(*p0) && isalpha(*p1)) {
40             if (xbm[*p0-'A']&xbm[*p1-'A']) {
                 cx = '*';
                 nm++;
             }
             else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
45                 cx = '.';
             else
                 cx = ' ';
          }
          else
50             cx = ' ';
          *px++ = cx;
      }
      *px++ = '\n';
      *px = '\0';
55  }

```

stars

60

**Table 1 (cont')**

```

/*
 * strip path or prefix from pn, return len: pr_align()
 */
static
5 stripname(pn)                                stripname
{
    char    *pn;    /* file name (may be path) */
    register char    *px, *py;
10     py = 0;
    for (px = pn; *px; px++)
        if (*px == '/')
            py = px + 1;
15     if (py)
        (void) strcpy(pn, py);
    return(strlen(pn));
}
20
25
30
35
40
45
50
55
60

```

**Table 1 (cont')**

```

/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
 * g_calloc() -- calloc() with error checkin
5  * readjumps() -- get the good jumps, from tmp file if necessary
 * writejumps() -- write a filled array of jumps to a tmp file: nw()
 */
#include "nw.h"
#include <sys/file.h>

10 char *jname = "/tmp/homgXXXXXX"; /* tmp file for jumps */
FILE *fj;

int cleanup(); /* cleanup tmp file */
15 long lseek();

/*
 * remove any tmp file if we blow
 */
20 cleanup(i)
    int i;
{
    if (fj)
        (void) unlink(jname);
25    exit(i);
}

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
30 char *
getseq(file, len)
35 char *file; /* file name */
    int *len; /* seq len */
{
    char line[1024], *pseq;
    register char *px, *py;
    int natgc, tlen;
    FILE *fp;

    if ((fp = fopen(file, "r")) == 0) {
        fprintf(stderr, "%s: can't read %s\n", prog, file);
        exit(1);
    }
    tlen = natgc = 0;
    while (fgets(line, 1024, fp)) {
        if (*line == ';' || *line == '<' || *line == '>')
            continue;
        for (px = line; *px != '\n'; px++)
            if (isupper(*px) || islower(*px))
                tlen++;
    }
    if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
        fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
        exit(1);
    }
    pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';
60

```

cleanup

getseq

Table 1 (cont')

...getseq

```

py = pseq + 4;
*len = tlen;
rewind(fp);
5
while (fgets(line, 1024, fp)) {
    if (*line == ';' || *line == '<' || *line == '>')
        continue;
    for (px = line; *px != '\n'; px++) {
10
        if (isupper(*px))
            *py++ = *px;
        else if (islower(*px))
            *py++ = toupper(*px);
        if (index("ATGCU", *(py-1)))
            natgc++;
15
    }
}
*py++ = '\0';
*py = '\0';
(void) fclose(fp);
dna = natgc > (tlen/3);
return(pseq+4);
}

25 char *
g_alloc(msg, nx, sz)
char *msg; /* program, calling routine */
int nx, sz; /* number and size of elements */
{
30 char *px, *calloc();

if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
    if (*msg) {
35
        fprintf(stderr, "%s: g_alloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
        exit(1);
    }
}
return(px);
}

40 /*
 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
 */
readjmps()
45 {
    int fd = -1;
    int siz, i0, i1;
    register i, j, xx;

50
    if (fj) {
        (void) fclose(fj);
        if ((fd = open(jname, O_RDONLY, 0)) < 0) {
            fprintf(stderr, "%s: can't open() %s\n", prog, jname);
            cleanup(1);
55
        }
    }
    for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
        while (1) {
60
            for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.xlj] >= xx; j--)
                ;

```

g\_alloc

readjmps

Table 1 (cont')

...readjumps

```

5      if (j < 0 && dx[dmax].offset && fj) {
          (void) lseek(fd, dx[dmax].offset, 0);
          (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
          (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
          dx[dmax].ijmp = MAXJMP-1;
      }
      else
          break;
10     }
    if (i >= JMPS) {
        fprintf(stderr, "%s: too many gaps in alignment\n", prog);
        cleanup(1);
    }
15     if (j >= 0) {
        siz = dx[dmax].jp.n[j];
        xx = dx[dmax].jp.x[j];
        dmax += siz;
        if (siz < 0) { /* gap in second seq */
20             pp[1].n[i1] = -siz;
            xx += siz;
            /* id = xx - yy + len1 - 1
             */
            pp[1].x[i1] = xx - dmax + len1 - 1;
            gapy++;
            ngapy -= siz;
            /* ignore MAXGAP when doing endgaps */
            siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
            i1++;
30         }
        else if (siz > 0) { /* gap in first seq */
            pp[0].n[i0] = siz;
            pp[0].x[i0] = xx;
            gapx++;
            ngapx += siz;
35         /* ignore MAXGAP when doing endgaps */
            siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
            i0++;
        }
40     }
    else
        break;
}

45     /* reverse the order of jmps
    */
    for (j = 0, i0--; j < i0; j++, i0--) {
        i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
        i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
50     }
    for (j = 0, i1--; j < i1; j++, i1--) {
        i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
        i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
55     }
    if (fd >= 0)
        (void) close(fd);
    if (fj) {
        (void) unlink(jname);
        fj = 0;
        offset = 0;
60     }
}

```



Table 1 (cont')

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */
5  writejumps(ix)
    int    ix;
    {
        char    *mktemp();
10         if (!fj) {
            if (mktemp(jname) < 0) {
                fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
                cleamp(1);
            }
15         if ((fj = fopen(jname, "w")) == 0) {
            fprintf(stderr, "%s: can't write %s\n", prog, jname);
            exit(1);
        }
20         (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
        (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
    }
}
25
30
35
40
45
50
55
60

```

**writejumps**

**Table 2**

PRO	XXXXXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXXYYYYYYY	(Length = 12 amino acids)

5    % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

10    5 divided by 15 = 33.3%

**Table 3**

PRO	XXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXXXXYYYZZYZ	(Length = 15 amino acids)

5    % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

10    5 divided by 10 = 50%

**Table 4**

PRO-DNA	NNNNNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNLLLLLLLLLL	(Length = 16 nucleotides)

5    % nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by  
ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

10    6 divided by 14 = 42.9%

**Table 5**

PRO-DNA	NNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLL	(Length = 9 nucleotides)

5    % nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

10    4 divided by 12 = 33.3%

## II. Compositions and Methods of the Invention

### A. Full-Length PRO Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding various PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ number is unique for any given DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by the full length native nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of PRO, will be referred to as "PRO/number", regardless of their origin or mode of preparation.

As disclosed in the Examples below, various cDNA clones have been deposited with the ATCC. The actual nucleotide sequences of those clones can readily be determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

### B. PRO Polypeptide Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO or in various domains of the PRO described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO that results in a change in the amino acid sequence of the PRO as compared with the native sequence PRO. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein. Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO polypeptide.

5 PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired  
10 termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial  
15 changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

	<u>Original Residue</u>	<u>Exemplary Substitutions</u>	<u>Preferred Substitutions</u>
5	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
	Cys (C)	ser	ser
10	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
	Ile (I)	leu; val; met; ala; phe;	
15		norleucine	leu
	Leu (L)	norleucine; ile; val;	
		met; ala; phe	ile
	Lys (K)	arg; gln; asn	arg
	Met (M)	leu; phe; ile	leu
20	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
	Ser (S)	thr	thr
	Thr (T)	ser	ser
	Trp (W)	tyr; phe	tyr
25	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe;	
		ala; norleucine	leu

Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl. Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al., Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA,



317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

### C. Modifications of PRO

Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidyl)propionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

Other modifications include deamidation of glutamyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the  $\alpha$ -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the

desired amino acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

5 Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

10 Another type of covalent modification of PRO comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

15 The PRO of the present invention may also be modified in a way to form a chimeric molecule comprising PRO fused to another, heterologous polypeptide or amino acid sequence.

20 In one embodiment, such a chimeric molecule comprises a fusion of the PRO with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO. The presence of such epitope-tagged forms of the PRO can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the 25 Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an  $\alpha$ -tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

30 In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred 35 embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

#### D. Preparation of PRO

The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO.

##### 1. Isolation of DNA Encoding PRO

DNA encoding PRO may be obtained from a cDNA library prepared from tissue believed to possess the PRO mRNA and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like <sup>32</sup>P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example,  $\text{CaCl}_2$ ,  $\text{CaPO}_4$ , liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan<sup>r</sup>*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7*

*ilvG kan'*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilum* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylophilic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylophilic Yeasts, 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol., 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

### 3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally

include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces*  $\alpha$ -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the  $2\mu$  plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature, 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the  $\beta$ -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid

promoters such as the tac promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO.

5 Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

10 Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

15 PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

20 Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin,  $\alpha$ -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 25 3' to the PRO coding sequence, but is preferably located at a site 5' from the promoter.

30 Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO.

35 Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

#### 4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

#### 5. Purification of Polypeptide

Forms of PRO may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO produced.

#### E. Uses for PRO

Nucleotide sequences (or their complement) encoding PRO have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO nucleic acid will also be useful for the preparation of PRO polypeptides by the recombinant techniques described herein.



The full-length native sequence PRO gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length PRO cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of PRO or PRO from other species) which have a desired sequence identity to the native PRO sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the full length native nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence PRO. By way of example, a screening method will comprise isolating the coding region of the PRO gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as  $^{32}\text{P}$  or  $^{35}\text{S}$ , or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the PRO gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below.

Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

Other useful fragments of the PRO nucleic acids include antisense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target PRO mRNA (sense) or PRO DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of PRO DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48:2659, 1988) and van der Krol et al. (BioTechniques 6:958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. The antisense oligonucleotides thus may be used to block expression of PRO proteins. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increase affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example,  $\text{CaPO}_4$ -mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see WO 90/13641).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

Antisense or sense RNA or DNA molecules are generally at least about 5 bases in length, about 10 bases in length, about 15 bases in length, about 20 bases in length, about 25 bases in length, about 30 bases in length, about 35 bases in length, about 40 bases in length, about 45 bases in length, about 50 bases in length, about 55 bases in length, about 60 bases in length, about 65 bases in length, about 70 bases in length, about 75 bases in length, about 80 bases in length, about 85 bases in length, about 90 bases in length, about 95 bases in length, about 100 bases in length, or more.

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO coding sequences.

Nucleotide sequences encoding a PRO can also be used to construct hybridization probes for mapping the gene which encodes that PRO and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

When the coding sequences for PRO encode a protein which binds to another protein (example, where the PRO is a receptor), the PRO can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor PRO can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds that mimic the biological activity of a native PRO or a receptor for PRO. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small

molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

Nucleic acids which encode PRO or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding PRO. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for PRO transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding PRO introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding PRO. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of PRO can be used to construct a PRO "knock out" animal which has a defective or altered gene encoding PRO as a result of homologous recombination between the endogenous gene encoding PRO and altered genomic DNA encoding PRO introduced into an embryonic stem cell of the animal. For example, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques. A portion of the genomic DNA encoding PRO can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of

the PRO polypeptide.

Nucleic acid encoding the PRO polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA. Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik *et al.*, Proc. Natl. Acad. Sci. USA 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau *et al.*, Trends in Biotechnology 11, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu *et al.*, J. Biol. Chem. 262, 4429-4432 (1987); and Wagner *et al.*, Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson *et al.*, Science 256, 808-813 (1992).

The PRO polypeptides described herein may also be employed as molecular weight markers for protein electrophoresis purposes and the isolated nucleic acid sequences may be used for recombinantly expressing those markers.

The nucleic acid molecules encoding the PRO polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each PRO nucleic acid molecule of the present invention can be used as a chromosome marker.

The PRO polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the PRO polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type. PRO nucleic acid molecules will find use for generating probes for PCR, Northern

analysis, Southern analysis and Western analysis.

The PRO polypeptides described herein may also be employed as therapeutic agents. The PRO polypeptides of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the PRO product hereof is combined in admixture with a pharmaceutically acceptable carrier vehicle. Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, PLURONICS™ or PEG.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution.

Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The route of administration is in accord with known methods, e.g. injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration, or by sustained release systems.

Dosages and desired drug concentrations of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary physician. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W. "The use of interspecies scaling in toxicokinetics" In Toxicokinetics and New Drug Development, Yacobi et al., Eds., Pergamon Press, New York 1989, pp. 42-96.

When *in vivo* administration of a PRO polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about 1 µg/kg/day to 10 mg/kg/day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Pat. Nos. 4,657,760; 5,206,344; or 5,225,212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue.

Where sustained-release administration of a PRO polypeptide is desired in a formulation with release characteristics suitable for the treatment of any disease or disorder requiring administration of the PRO

polypeptide, microencapsulation of the PRO polypeptide is contemplated. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon- (rhIFN- ), interleukin-2, and MN rgp120. Johnson et al., Nat. Med., 2:795-799 (1996); Yasuda, Biomed. Ther., 27:1221-1223 (1993); Hora et al., Bio/Technology, 8:755-758 (1990); Cleland, "Design and Production of Single Immunization Vaccines Using Polylactide Polyglycolide Microsphere Systems," in Vaccine Design: The Subunit and Adjuvant Approach, Powell and Newman, eds, (Plenum Press: New York, 1995), pp. 439-462; WO 97/03692, WO 96/40072, WO 96/07399; and U.S. Pat. No. 5,654,010.

The sustained-release formulations of these proteins were developed using poly-lactic-coglycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids, can be cleared quickly within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its molecular weight and composition. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer," in: M. Chasin and R. Langer (Eds.), Biodegradable Polymers as Drug Delivery Systems (Marcel Dekker: New York, 1990), pp. 1-41.

This invention encompasses methods of screening compounds to identify those that mimic the PRO polypeptide (agonists) or prevent the effect of the PRO polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the PRO polypeptides encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a PRO polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the PRO polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the PRO polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for  $\beta$ -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the PRO polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., Current Protocols in Immun., 1(2): Chapter 5 (1991).

Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO polypeptide. Transfected cells that are grown on glass slides are exposed to labeled PRO polypeptide. The PRO polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, labeled PRO polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with labeled PRO polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with PRO polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the PRO polypeptide.

Another potential PRO polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature PRO polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby preventing transcription and the production of the PRO polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the PRO polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988)). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the PRO



polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Rossi, Current Biology, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

Diagnostic and therapeutic uses of the herein disclosed molecules may also be based upon the positive functional assay hits disclosed and described below.

#### F. Anti-PRO Antibodies

The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

##### 1. Polyclonal Antibodies

The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

## 2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103]. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against PRO. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, supra]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., *supra*] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

*In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

### 3. Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub> or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones

et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeven et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner et al., J. Immunol., 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks *et al.*, Bio/Technology 10, 779-783 (1992); Lonberg *et al.*, Nature 368 856-859 (1994); Morrison, Nature 368, 812-13 (1994); Fishwild *et al.*, Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

The antibodies may also be affinity matured using known selection and/or mutagenesis methods as described above. Preferred affinity matured antibodies have an affinity which is five times, more preferably 10 times, even more preferably 20 or 30 times greater than the starting antibody (generally murine, humanized or human) from which the matured antibody is prepared.

#### 4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain

pairs, where the two heavy chains have different specificities [Milstein and Cuello, *Nature*, 305:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., *EMBO J.*, 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., *Methods in Enzymology*, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')<sub>2</sub> bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., *Science* 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')<sub>2</sub> fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med.*, 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')<sub>2</sub> molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various technique for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny *et al.*, *J. Immunol.* 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger *et al.*, *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain ( $V_H$ ) connected to a light-chain variable domain ( $V_L$ ) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the  $V_H$  and  $V_L$  domains of one fragment are forced to pair with the complementary  $V_L$  and  $V_H$  domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber *et al.*, *J. Immunol.* 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.*, *J. Immunol.* 147:60 (1991).

Exemplary bispecific antibodies may bind to two different epitopes on a given PRO polypeptide herein. Alternatively, an anti-PRO polypeptide arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular PRO polypeptide. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express a particular PRO polypeptide. These antibodies possess a PRO-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the PRO polypeptide and further binds tissue factor (TF).

#### 5. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

#### 6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, e.g., the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be

introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, J. Exp Med., **176**: 1191-1195 (1992) and Shopes, J. Immunol., **148**: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.* Cancer Research, **53**: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, Anti-Cancer Drug Design, **3**: 219-230 (1989).

#### 7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include <sup>212</sup>Bi, <sup>131</sup>I, <sup>131</sup>In, <sup>90</sup>Y, and <sup>186</sup>Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, **238**: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

#### 8. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, **77**: 4030 (1980); and U.S. Pat. Nos.

4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.*, *J. Biol. Chem.*, 257: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon *et al.*, *J. National Cancer Inst.*, 81(19): 1484 (1989).

#### 9. Pharmaceutical Compositions of Antibodies

Antibodies specifically binding a PRO polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders in the form of pharmaceutical compositions.

If the PRO polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, *e.g.*, Marasco *et al.*, *Proc. Natl. Acad. Sci. USA*, 90: 7889-7893 (1993). The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, *supra*.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and  $\gamma$  ethyl-L-glutamate, non-degradable ethylene-vinyl



acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

#### G. Uses for anti-PRO Antibodies

The anti-PRO antibodies of the invention have various utilities. For example, anti-PRO antibodies may be used in diagnostic assays for PRO, *e.g.*, detecting its expression (and in some cases, differential expression) in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, Monoclonal Antibodies: A Manual of Techniques, CRC Press, Inc. (1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as <sup>3</sup>H, <sup>14</sup>C, <sup>32</sup>P, <sup>35</sup>S, or <sup>125</sup>I, a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter et al., Nature, 144:945 (1962); David et al., Biochemistry, 13:1014 (1974); Pain et al., J. Immunol. Meth., 40:219 (1981); and Nygren, J. Histochem. and Cytochem., 30:407 (1982).

Anti-PRO antibodies also are useful for the affinity purification of PRO from recombinant cell culture or natural sources. In this process, the antibodies against PRO are immobilized on a suitable support, such as Sephadex resin or filter paper, using methods well known in the art. The immobilized antibody then is contacted with a sample containing the PRO to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the PRO, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent that will release the PRO from the antibody.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

### EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

#### EXAMPLE 1: Extracellular Domain Homology Screening to Identify Novel Polypeptides and cDNA Encoding Therefor

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (e.g., Dayhoff, GenBank), and proprietary databases (e.g. LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST-2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA).

Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of BLAST or BLAST-2 and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for a PRO polypeptide. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

**EXAMPLE 2: Isolation of cDNA clones by Amylase Screening****1. Preparation of oligo dT primed cDNA library**

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System).

5 In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the Sall/NotI linker cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

**2. Preparation of random primed cDNA library**

10 A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA was sized to 500-1000 bp, linker cDNA with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI  
15 cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

**3. Transformation and Detection**

20 DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was  
25 added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, e.g. CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

30 The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

35 The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, ura3-52, leu2-3, leu2-112, his3-11, his3-15, MAL<sup>+</sup>, SUC<sup>+</sup>, GAL<sup>+</sup>. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in *sec71*, *sec72*, *sec62*, with truncated *sec71* being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins

implicated in this post translation pathway (e.g., SEC61p, SEC72p, SEC62p, SEC63p, TDJ1p or SSA1p-4p) or the complex formation of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

Transformation was performed based on the protocol outlined by Gietz et al., Nucl. Acid. Res., 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser et al., Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about  $2 \times 10^6$  cells/ml (approx.  $OD_{600}=0.1$ ) into fresh YEPD broth (500 ml) and regrown to  $1 \times 10^7$  cells/ml (approx.  $OD_{600}=0.4-0.5$ ).

The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM  $Li_2OOCCH_3$ ), and resuspended into LiAc/TE (2.5 ml).

Transformation took place by mixing the prepared cells (100  $\mu$ l) with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1  $\mu$ g, vol. < 10  $\mu$ l) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600  $\mu$ l, 40% polyethylene glycol-4000, 10 mM Tris-HCl, 1 mM EDTA, 100 mM  $Li_2OOCCH_3$ , pH 7.5) was added. This mixture was gently mixed and incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes, and the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500  $\mu$ l, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200  $\mu$ l) were spread onto the selective media previously prepared in 150 mm growth plates (VWR).

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser et al., Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-210 (1994). Transformants were grown at 30°C for 2-3 days.

The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely et al., Anal. Biochem., 172:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

#### 4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30  $\mu$ l) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5  $\mu$ l) was used as a template for the PCR reaction in a 25  $\mu$ l volume containing: 0.5  $\mu$ l Klentaq (Clontech, Palo Alto, CA); 4.0  $\mu$ l 10 mM dNTP's (Perkin Elmer-Cetus); 2.5  $\mu$ l Kentaq buffer (Clontech); 0.25  $\mu$ l forward oligo 1; 0.25  $\mu$ l reverse oligo 2; 12.5  $\mu$ l distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAACGACGGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:169)

The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:170)

PCR was then performed as follows:

- |    |               |          |                  |
|----|---------------|----------|------------------|
| a. |               | Denature | 92°C, 5 minutes  |
| b. | 3 cycles of:  | Denature | 92°C, 30 seconds |
|    |               | Anneal   | 59°C, 30 seconds |
|    |               | Extend   | 72°C, 60 seconds |
| c. | 3 cycles of:  | Denature | 92°C, 30 seconds |
|    |               | Anneal   | 57°C, 30 seconds |
|    |               | Extend   | 72°C, 60 seconds |
| d. | 25 cycles of: | Denature | 92°C, 30 seconds |
|    |               | Anneal   | 55°C, 30 seconds |
|    |               | Extend   | 72°C, 60 seconds |
| e. |               | Hold     | 4°C              |

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present. Typically, the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5  $\mu$ l) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook et al., *supra*. Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

#### EXAMPLE 3: Isolation of cDNA Clones Using Signal Algorithm Analysis

Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine

codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals. Use of this algorithm resulted in the identification of numerous polypeptide-encoding nucleic acid sequences.

#### EXAMPLE 4: Isolation of cDNA Clones Encoding Human PRO Polypeptides

Using the techniques described in Examples 1 to 3 above, numerous full-length cDNA clones were identified as encoding PRO polypeptides as disclosed herein. These cDNAs were then deposited under the terms of the Budapest Treaty with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC) as shown in Table 7 below.

Table 7

	<u>Material</u>	<u>ATCC Dep. No.</u>	<u>Deposit Date</u>
15	DNA26843-1389	203099	August 4, 1998
	DNA30867-1335	209807	April 28, 1998
	DNA34431-1177	209399	October 17, 1997
	DNA38268-1188	209421	October 28, 1997
20	DNA40621-1440	209922	June 2, 1998
	DNA40625-1189	209788	April 21, 1998
	DNA45409-2511	203579	January 12, 1999
	DNA45495-1550	203156	August 25, 1998
	DNA49820-1427	209932	June 2, 1998
25	DNA56406-1704	203478	November 17, 1998
	DNA56410-1414	209923	June 2, 1998
	DNA56436-1448	209902	May 27, 1998
	DNA56855-1447	203004	June 23, 1998
	DNA56860-1510	209952	June 9, 1998
30	DNA56862-1343	203174	September 1, 1998
	DNA56868-1478	203024	June 23, 1998
	DNA56869-1545	203161	August 25, 1998
	DNA57704-1452	209953	June 9, 1998
	DNA58723-1588	203133	August 18, 1998
35	DNA57827-1493	203045	July 1, 1998
	DNA58737-1473	203136	August 18, 1998
	DNA58846-1409	209957	June 9, 1998
	DNA58850-1495	209956	June 9, 1998
	DNA58855-1422	203018	June 23, 1998
40	DNA59211-1450	209960	June 9, 1998
	DNA59212-1627	203245	September 9, 1998
	DNA59213-1487	209959	June 9, 1998
	DNA59605-1418	203005	June 23, 1998
	DNA59609-1470	209963	June 9, 1998
45	DNA59610-1556	209990	June 16, 1998
	DNA59837-2545	203658	February 9, 1999
	DNA59844-2542	203650	February 9, 1999
	DNA59854-1459	209974	June 16, 1998

Table 7 (cont')

	DNA60625-1507	209975	June 16, 1998
	DNA60629-1481	209979	June 16, 1998
	DNA61755-1554	203112	August 11, 1998
5	DNA62812-1594	203248	September 9, 1998
	DNA62815-1576	203247	September 9, 1998
	DNA64881-1602	203240	September 9, 1998
	DNA64886-1601	203241	September 9, 1998
	DNA64902-1667	203317	October 6, 1998
10	DNA64950-1590	203224	September 15, 1998
	DNA65403-1565	203230	September 15, 1998
	DNA66308-1537	203159	August 25, 1998
	DNA66519-1535	203236	September 15, 1998
	DNA66521-1583	203225	September 15, 1998
15	DNA66658-1584	203229	September 15, 1998
	DNA66660-1585	203279	September 22, 1998
	DNA66663-1598	203268	September 22, 1998
	DNA66674-1599	203281	September 22, 1998
	DNA68862-2546	203652	February 9, 1999
20	DNA68866-1644	203283	September 22, 1998
	DNA68871-1638	203280	September 22, 1998
	DNA68880-1676	203319	October 6, 1998
	DNA68883-1691	203535	December 15, 1998
	DNA68885-1678	203311	October 6, 1998
25	DNA71277-1636	203285	September 22, 1998
	DNA73727-1673	203459	November 3, 1998
	DNA73734-1680	203363	October 20, 1998
	DNA73735-1681	203356	October 20, 1998
	DNA76393-1664	203323	October 6, 1998
30	DNA77301-1708	203407	October 27, 1998
	DNA77568-1626	203134	August 18, 1998
	DNA77626-1705	203536	December 15, 1998
	DNA81754-2532	203542	December 15, 1998
	DNA81757-2512	203543	December 15, 1998
35	DNA82302-2529	203534	December 15, 1998
	DNA82340-2530	203547	December 22, 1998
	DNA83500-2506	203391	October 29, 1998
	DNA84920-2614	203966	April 27, 1999
	DNA85066-2534	203588	January 12, 1999
40	DNA86571-2551	203660	February 9, 1999
	DNA87991-2540	203656	February 9, 1999
	DNA92238-2539	203602	January 20, 1999
	DNA96042-2682	PTA-382	July 20, 1999
	DNA96787-2534	203589	January 12, 1999
45	DNA125185-2806	PTA-1031	December 7, 1999
	DNA147531-2821	PTA-1185	January 11, 2000
	DNA115291-2681	PTA-202	June 8, 1999
	DNA164625-28890	PTA-1535	March 21, 2000
	DNA131639-2874	PTA-1784	April 25, 2000
50	DNA79230-2525	203549	December 22, 1998

These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The

deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC § 122 and the Commissioner's rules pursuant thereto (including 37 CFR § 1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

#### EXAMPLE 5: Use of PRO as a hybridization probe

The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe. DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can then be identified using standard techniques known in the art.

#### EXAMPLE 6: Expression of PRO in *E. coli*

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.



The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.<sub>600</sub> of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 0.71 g sodium citrate•2H<sub>2</sub>O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO<sub>4</sub>) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

*E. coli* paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The

refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### EXAMPLE 7: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., *supra*. The resulting vector is called pRK5-PRO.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-PRO DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya et al., *Cell*, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl<sub>2</sub>. To this mixture is added, dropwise, 500 µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO<sub>4</sub>, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/ml <sup>35</sup>S-cysteine and 200 µCi/ml <sup>35</sup>S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in

serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Sompanyrac et al., Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700  $\mu$ g pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5  $\mu$ g/ml bovine insulin and 0.1  $\mu$ g/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as  $\text{CaPO}_4$  or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as  $^{35}\text{S}$ -methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by  $\text{Ni}^{2+}$ -chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect<sup>®</sup> (Quiagen), Dosper<sup>®</sup> or Fugene<sup>®</sup> (Boehringer Mannheim). The cells are grown as described in Lucas et al., *supra*. Approximately  $3 \times 10^7$  cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2  $\mu$ m filtered PS20 with 5% 0.2  $\mu$ m diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with  $3 \times 10^5$  cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at  $1.2 \times 10^6$  cells/mL. On day 0, the cell number pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22  $\mu$ m filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275  $\mu$ L of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

**EXAMPLE 8: Expression of PRO in Yeast**

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

**EXAMPLE 9: Expression of PRO in Baculovirus-Infected Insect Cells**

The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (PharMingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilly et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-his tagged PRO can then be purified, for example, by Ni<sup>2+</sup>-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl<sub>2</sub>; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 μm

filter. A  $\text{Ni}^{2+}$ -NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline  $A_{280}$  with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching  
5  $A_{280}$  baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with  $\text{Ni}^{2+}$ -NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His<sub>10</sub>-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known  
10 chromatography techniques, including for instance, Protein A or protein G column chromatography.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### EXAMPLE 10: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

15 Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

20 Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice  
25 by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells  
30 which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

35 The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively,

affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

**EXAMPLE 11: Purification of PRO Polypeptides Using Specific Antibodies**

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

**EXAMPLE 12: Drug Screening**

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with

an PRO polypeptide or fragment thereof and assaying (I) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

#### EXAMPLE 13: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 2: 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic



antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

#### EXAMPLE 14: Pericyte c-Fos Induction (Assay 93)

This assay shows that certain polypeptides of the invention act to induce the expression of c-fos in pericyte cells and, therefore, are useful not only as diagnostic markers for particular types of pericyte-associated tumors but also for giving rise to antagonists which would be expected to be useful for the therapeutic treatment of pericyte-associated tumors. Induction of c-fos expression in pericytes is also indicative of the induction of angiogenesis and, as such, PRO polypeptides capable of inducing the expression of c-fos would be expected to be useful for the treatment of conditions where induced angiogenesis would be beneficial including, for example, wound healing, and the like. Specifically, on day 1, pericytes are received from VEC Technologies and all but 5 ml of media is removed from flask. On day 2, the pericytes are trypsinized, washed, spun and then plated onto 96 well plates. On day 7, the media is removed and the pericytes are treated with 100  $\mu$ l of PRO polypeptide test samples and controls (positive control = DME+5% serum +/- PDGF at 500 ng/ml; negative control = protein 32). Replicates are averaged and SD/CV are determined. Fold increase over Protein 32 (buffer control) value indicated by chemiluminescence units (RLU) luminometer reading verses frequency is plotted on a histogram. Two-fold above Protein 32 value is considered positive for the assay. ASY Matrix: Growth media = low glucose DMEM = 20% FBS + 1X pen strep + 1X fungizone. Assay Media = low glucose DMEM +5% FBS.

The following polypeptides tested positive in this assay: PRO1347 and PRO1340.

#### EXAMPLE 15: Ability of PRO Polypeptides to Stimulate the Release of Proteoglycans from Cartilage (Assay 97)

The ability of various PRO polypeptides to stimulate the release of proteoglycans from cartilage tissue was tested as follows.

The metacarpophalangeal joint of 4-6 month old pigs was aseptically dissected, and articular cartilage was removed by free hand slicing being careful to avoid the underlying bone. The cartilage was minced and cultured in bulk for 24 hours in a humidified atmosphere of 95% air, 5% CO<sub>2</sub> in serum free (SF) media (DME/F12 1:1) with 0.1% BSA and 100U/ml penicillin and 100 $\mu$ g/ml streptomycin. After washing three times, approximately 100 mg of articular cartilage was aliquoted into micronics tubes and incubated for an additional 24 hours in the above SF media. PRO polypeptides were then added at 1% either alone or in combination with 18 ng/ml interleukin-1 $\alpha$ , a known stimulator of proteoglycan release from cartilage tissue.

The supernatant was then harvested and assayed for the amount of proteoglycans using the 1,9-dimethyl-methylene blue (DMB) colorimetric assay (Farndale and Buttle, *Biochem. Biophys. Acta* 883:173-177 (1985)). A positive result in this assay indicates that the test polypeptide will find use, for example, in the treatment of sports-related joint problems, articular cartilage defects, osteoarthritis or rheumatoid arthritis.

When various PRO polypeptides were tested in the above assay, the polypeptides demonstrated a marked ability to stimulate release of proteoglycans from cartilage tissue both basally and after stimulation with interleukin-1 $\alpha$  and at 24 and 72 hours after treatment, thereby indicating that these PRO polypeptides are useful for stimulating proteoglycan release from cartilage tissue. As such, these PRO polypeptides are useful for the treatment of sports-related joint problems, articular cartilage defects, osteoarthritis or rheumatoid arthritis. The polypeptides testing positive in this assay are: PRO1565, PRO1693, PRO1801 and PRO10096.

#### EXAMPLE 16: Detection of Polypeptides That Affect Glucose or FFA Uptake in Skeletal Muscle (Assay 106)

This assay is designed to determine whether PRO polypeptides show the ability to affect glucose or FFA uptake by skeletal muscle cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of disorders where either the stimulation or inhibition of glucose uptake by skeletal muscle would be beneficial including, for example, diabetes or hyper- or hypo-insulinemia.

In a 96 well format, PRO polypeptides to be assayed are added to primary rat differentiated skeletal muscle, and allowed to incubate overnight. Then fresh media with the PRO polypeptide and +/- insulin are added to the wells. The sample media is then monitored to determine glucose and FFA uptake by the skeletal muscle cells. The insulin will stimulate glucose and FFA uptake by the skeletal muscle, and insulin in media without the PRO polypeptide is used as a positive control, and a limit for scoring. As the PRO polypeptide being tested may either stimulate or inhibit glucose and FFA uptake, results are scored as positive in the assay if greater than 1.5 times or less than 0.5 times the insulin control.

The following PRO polypeptides tested positive as either stimulators or inhibitors of glucose and/or FFA uptake in this assay: PRO4405.

#### EXAMPLE 17: Identification of PRO Polypeptides That Stimulate TNF- $\alpha$ Release In Human Blood (Assay 128)

This assay shows that certain PRO polypeptides of the present invention act to stimulate the release of TNF- $\alpha$  in human blood. PRO polypeptides testing positive in this assay are useful for, among other things, research purposes where stimulation of the release of TNF- $\alpha$  would be desired and for the therapeutic treatment of conditions wherein enhanced TNF- $\alpha$  release would be beneficial. Specifically, 200  $\mu$ l of human blood supplemented with 50mM Hepes buffer (pH 7.2) is aliquotted per well in a 96 well test plate. To each well is then added 300 $\mu$ l of either the test PRO polypeptide in 50 mM Hepes buffer (at various concentrations) or 50 mM Hepes buffer alone (negative control) and the plates are incubated at 37°C for 6 hours. The samples are then centrifuged and 50 $\mu$ l of plasma is collected from each well and tested for the presence of TNF- $\alpha$  by ELISA assay. A positive in the assay is a higher amount of TNF- $\alpha$  in the PRO polypeptide treated samples as compared to the negative control samples.

The following PRO polypeptides tested positive in this assay: PRO263, PRO295, PRO1282, PRO1063, PRO1356, PRO3543, and PRO5990.

**EXAMPLE 18: Tumor Versus Normal Differential Tissue Expression Distribution**

Oligonucleotide probes were constructed from some of the PRO polypeptide-encoding nucleotide sequences shown in the accompanying figures for use in quantitative PCR amplification reactions. The oligonucleotide probes were chosen so as to give an approximately 200-600 base pair amplified fragment from the 3' end of its associated template in a standard PCR reaction. The oligonucleotide probes were employed in standard quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acid in the various tumor and normal tissues tested.  $\beta$ -actin was used as a control to assure that equivalent amounts of nucleic acid was used in each reaction. Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. These assays provided the following results.

	<u>Molecule</u>	<u>is more highly expressed in:</u>	<u>as compared to:</u>
20	DNA26843-1389	normal lung rectum tumor	lung tumor normal rectum
	DNA30867-1335	normal kidney	kidney tumor
25	DNA40621-1440	normal lung	lung tumor
	DNA40625-1189	normal lung	lung tumor
	DNA45409-2511	melanoma tumor	normal skin
30	DNA56406-1704	kidney tumor normal skin	normal kidney melanoma tumor
	DNA56410-1414	normal stomach	stomach tumor
35	DNA56436-1448	normal skin	melanoma tumor
	DNA56855-1447	normal esophagus rectum tumor	esophageal tumor normal rectum
40	DNA56860-1510	normal kidney rectum tumor	kidney tumor normal rectum
45	DNA56862-1343	kidney tumor normal lung	normal kidney lung tumor

	<u>Molecule</u>	<u>is more highly expressed in:</u>	<u>as compared to:</u>
	DNA56868-1478	normal stomach normal lung	stomach tumor lung tumor
5	DNA56869-1545	normal esophagus normal skin	esophageal tumor melanoma tumor
	DNA57704-1452	normal stomach rectum tumor	stomach tumor normal rectum
10	DNA58723-1588	normal stomach kidney tumor normal skin	stomach tumor normal kidney melanoma tumor
15	DNA57827-1493	normal stomach normal skin	stomach tumor melanoma tumor
	DNA58737-1473	esophageal tumor normal stomach	normal esophagus stomach tumor
20	DNA58846-1409	lung tumor	normal lung
	DNA58850-1495	esophageal tumor kidney tumor	normal esophagus normal kidney
25	DNA58855-1422	normal stomach rectum tumor	stomach tumor normal rectum
	DNA59211-1450	normal kidney	kidney tumor
30	DNA59212-1627	normal skin	melanoma tumor
	DNA59213-1487	normal stomach normal skin	stomach tumor melanoma tumor
35	DNA59605-1418	melanoma tumor	normal skin
	DNA59609-1470	esophageal tumor	normal esophagus
40	DNA59610-1556	esophageal tumor lung tumor normal skin	normal esophagus normal lung melanoma tumor
	DNA59837-2545	normal skin	melanoma tumor
45	DNA59844-2542	normal skin esophageal tumor	melanoma tumor normal esophagus
50	DNA59854-1459	normal esophagus stomach tumor normal lung	esophageal tumor normal stomach lung tumor
	DNA60625-1507	normal lung	lung tumor
55	DNA60629-1481	normal esophagus normal rectum	esophageal tumor rectum tumor

	<u>Molecule</u>	<u>is more highly expressed in:</u>	<u>as compared to:</u>
	DNA61755-1554	normal stomach kidney tumor	stomach tumor normal kidney
5	DNA62812-1594	normal stomach normal lung normal rectum normal skin	stomach tumor lung tumor rectum tumor melanoma tumor
10	DNA62815-1576	esophageal tumor	normal esophagus
	DNA64881-1602	normal stomach normal lung	stomach tumor lung tumor
15	DNA64902-1667	esophageal tumor kidney tumor	normal esophagus normal kidney
	DNA65403-1565	normal esophagus	esophageal tumor
20	DNA66308-1537	normal lung	lung tumor
	DNA66519-1535	kidney tumor	normal kidney
25	DNA66521-1583	normal esophagus normal stomach normal lung normal rectum normal skin	esophageal tumor stomach tumor lung tumor rectum tumor melanoma tumor
30	DNA66658-1584	normal lung melanoma tumor	lung tumor normal skin
	DNA66660-1585	lung tumor	normal lung
35	DNA66674-1599	kidney tumor normal lung	normal kidney lung tumor
	DNA68862-2546	melanoma tumor	normal skin
40	DNA68866-1644	normal stomach	stomach tumor
	DNA68871-1638	lung tumor normal skin	normal lung melanoma tumor
45	DNA68880-1676	normal lung normal skin	lung tumor melanoma tumor
	DNA68883-1691	esophageal tumor	normal esophagus
50	DNA68885-1678	lung tumor	normal lung
	DNA71277-1636	normal stomach	stomach tumor
55	DNA73734-1680	normal lung	lung tumor

	<u>Molecule</u>	<u>is more highly expressed in:</u>	<u>as compared to:</u>
	DNA73735-1681	esophageal tumor normal kidney lung tumor normal skin	normal esophagus kidney tumor normal lung melanoma tumor
5			
	DNA76393-1664	esophageal tumor stomach tumor lung tumor rectum tumor	normal esophagus normal stomach normal lung normal rectum
10			
	DNA77568-1626	normal stomach lung tumor	stomach tumor normal lung
	DNA77626-1705	normal rectum	rectum tumor
15			
	DNA81754-2532	normal skin	melanoma tumor
	DNA81757-2512	esophageal tumor normal stomach melanoma tumor	normal esophagus stomach tumor normal skin
20			
	DNA82302-2529	normal stomach normal lung	stomach tumor lung tumor
	DNA82340-2530	normal esophagus	esophageal tumor
25			
	DNA85066-2534	lung tumor normal skin	normal lung melanoma tumor
	DNA87991-2540	esophageal tumor	normal esophagus
30			
	DNA92238-2539	normal skin	melanoma tumor
	DNA96787-2534	normal kidney	kidney tumor
35			

**EXAMPLE 19: Identification of Receptor/Ligand Interactions**

In this assay, various PRO polypeptides are tested for ability to bind to a panel of potential receptor or ligand molecules for the purpose of identifying receptor/ligand interactions. The identification of a ligand for a known receptor, a receptor for a known ligand or a novel receptor/ligand pair is useful for a variety of indications including, for example, targeting bioactive molecules (linked to the ligand or receptor) to a cell known to express the receptor or ligand, use of the receptor or ligand as a reagent to detect the presence of the ligand or receptor in a composition suspected of containing the same, wherein the composition may comprise cells suspected of expressing the ligand or receptor, modulating the growth of or another biological or immunological activity of a cell known to express or respond to the receptor or ligand, modulating the immune response of cells or toward cells that express the receptor or ligand, allowing the preparation of agonists, antagonists and/or antibodies directed against the receptor or ligand which will modulate the growth of or a biological or immunological activity of a cell expressing the receptor or ligand, and various other indications which will be readily apparent to the ordinarily skilled artisan.

The assay is performed as follows. A PRO polypeptide of the present invention suspected of being a ligand for a receptor is expressed as a fusion protein containing the Fc domain of human IgG (an immunoadhesin). Receptor-ligand binding is detected by allowing interaction of the immunoadhesin polypeptide with cells (e.g. Cos cells) expressing candidate PRO polypeptide receptors and visualization of bound immunoadhesin with fluorescent reagents directed toward the Fc fusion domain and examination by microscope.

5 Cells expressing candidate receptors are produced by transient transfection, in parallel, of defined subsets of a library of cDNA expression vectors encoding PRO polypeptides that may function as receptor molecules. Cells are then incubated for 1 hour in the presence of the PRO polypeptide immunoadhesin being tested for possible receptor binding. The cells are then washed and fixed with paraformaldehyde. The cells are then incubated with fluorescent conjugated antibody directed against the Fc portion of the PRO polypeptide immunoadhesin (e.g. FITC conjugated goat anti-human-Fc antibody). The cells are then washed again and examined by microscope. A positive interaction is judged by the presence of fluorescent labeling of cells transfected with cDNA encoding a particular PRO polypeptide receptor or pool of receptors and an absence of similar fluorescent labeling of similarly prepared cells that have been transfected with other cDNA or pools of cDNA. If a defined pool of cDNA expression vectors is judged to be positive for interaction with a PRO polypeptide immunoadhesin, the individual cDNA species that comprise the pool are tested individually (the pool is "broken down") to determine the specific cDNA that encodes a receptor able to interact with the PRO polypeptide immunoadhesin.

In another embodiment of this assay, an epitope-tagged potential ligand PRO polypeptide (e.g. 8 histidine "His" tag) is allowed to interact with a panel of potential receptor PRO polypeptide molecules that have been expressed as fusions with the Fc domain of human IgG (immunoadhesins). Following a 1 hour co-incubation with the epitope tagged PRO polypeptide, the candidate receptors are each immunoprecipitated with protein A beads and the beads are washed. Potential ligand interaction is determined by western blot analysis of the immunoprecipitated complexes with antibody directed towards the epitope tag. An interaction is judged to occur if a band of the anticipated molecular weight of the epitope tagged protein is observed in the western blot analysis with a candidate receptor, but is not observed to occur with the other members of the panel of potential receptors.

Using these assays, the following receptor/ligand interactions have been herein identified:

- (1) PRO10272 binds to PRO5801.
- (2) PRO20110 binds to the human IL-17 receptor (Yao et al., *Cytokine* 9(11):794-800 (1997); also herein designated as PRO1) and to PRO20040.
- (3) PRO10096 binds to PRO20233.
- (4) PRO19670 binds to PRO1890.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the

claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.



WHAT IS CLAIMED IS:

1. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16),  
5 Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54),  
10 Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92),  
15 Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure  
20 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) and Figure 168 (SEQ ID NO:168).
2. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure  
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73 (SEQ ID NO:73), Figure 75 (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:1390), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165) and Figure 167 (SEQ ID NO:167).

3. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figure 75 (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:1390), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155),

Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165) and Figure 167 (SEQ ID NO:167).

4. Isolated nucleic acid having at least 80% nucleic acid sequence identity to the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

5. A vector comprising the nucleic acid of Claim 1.

6. The vector of Claim 5 operably linked to control sequences recognized by a host cell transformed with the vector.

7. A host cell comprising the vector of Claim 5.

8. The host cell of Claim 7, wherein said cell is a CHO cell.

9. The host cell of Claim 7, wherein said cell is an *E. coli*.

10. The host cell of Claim 7, wherein said cell is a yeast cell.

11. A process for producing a PRO polypeptides comprising culturing the host cell of Claim 7 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

12. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102

(SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) and Figure 168 (SEQ ID NO:168).

13. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence encoded by the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

14. A chimeric molecule comprising a polypeptide according to Claim 12 fused to a heterologous amino acid sequence.

15. The chimeric molecule of Claim 14, wherein said heterologous amino acid sequence is an epitope tag sequence.

16. The chimeric molecule of Claim 14, wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.

17. An antibody which specifically binds to a polypeptide according to Claim 12.

18. The antibody of Claim 17, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.

19. Isolated nucleic acid having at least 80% nucleic acid sequence identity to:

(a) a nucleotide sequence encoding the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure

58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide;

(b) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156),

Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), with its associated signal peptide;  
or

- (c) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide.

20. An isolated polypeptide having at least 80% amino acid sequence identity to:
- (a) an amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58

(SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide;

(b) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure

158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), with its associated signal peptide;  
or

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166) or Figure 168 (SEQ ID NO:168), lacking its associated signal peptide.

21. A method of detecting a polypeptide designated as A, B, C or D in a sample suspected of containing an A, B, C or D polypeptide, said method comprising contacting said sample with a polypeptide designated herein as E, F, G, H or I and determining the formation of a A/E, B/F, B/G, C/H or D/I polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of an A, B, C or D polypeptide in said sample and wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

22. The method according to Claim 21, wherein said sample comprises cells suspected of expressing said A, B, C or D polypeptide.



23. The method according to Claim 21, wherein said E, F, G, H or I polypeptide is labeled with a detectable label.

24. The method according to Claim 21, wherein said E, F, G, H or I polypeptide is attached to a solid support.

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25. A method of detecting a polypeptide designated as E, F, G, H or I in a sample suspected of containing an E, F, G, H or I polypeptide, said method comprising contacting said sample with a polypeptide designated herein as A, B, C or D and determining the formation of a A/E, B/F, B/G, C/H or D/I polypeptide conjugate in said sample, wherein the formation of said conjugate is indicative of the presence of an A, B, C or D polypeptide in said sample and wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

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26. The method according to Claim 25, wherein said sample comprises cells suspected of expressing said E, F, G, H or I polypeptide.

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27. The method according to Claim 25, wherein said A, B, C or D polypeptide is labeled with a detectable label.

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28. The method according to Claim 25, wherein said A, B, C or D polypeptide is attached to a solid support.

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29. A method of linking a bioactive molecule to a cell expressing a polypeptide designated as A, B, C or D, said method comprising contacting said cell with a polypeptide designated as E, F, G, H or I that is bound to said bioactive molecule and allowing said A, B, C or D and said E, F, G, H or I polypeptides to bind to one another, thereby linking said bioactive molecules to said cell, wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

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30. The method according to Claim 29, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

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31. The method according to Claim 29, wherein said bioactive molecule causes the death of said cell.

32. A method of linking a bioactive molecule to a cell expressing a polypeptide designated as E, F, G, H or I, said method comprising contacting said cell with a polypeptide designated as A, B, C or D that is bound to said bioactive molecule and allowing said A, B, C or D and said E, F, G, H or I polypeptides to bind to one another, thereby linking said bioactive molecules to said cell, wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

33. The method according to Claim 32, wherein said bioactive molecule is a toxin, a radiolabel or an antibody.

34. The method according to Claim 32, wherein said bioactive molecule causes the death of said cell.

35. A method of modulating at least one biological activity of a cell expressing a polypeptide designated as A, B, C or D, said method comprising contacting said cell with a polypeptide designated as E, F, G, H or I or an anti-A, B, C or D polypeptide antibody, whereby said E, F, G, H or I polypeptide or anti-A, B, C or D polypeptide antibody binds to said A, B, C or D polypeptide, thereby modulating at least one biological activity of said cell, wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

36. The method according to Claim 35, wherein said cell is killed.

37. A method of modulating at least one biological activity of a cell expressing a polypeptide designated as E, F, G, H or I, said method comprising contacting said cell with a polypeptide designated as A, B, C or D or an anti-E, F, G, H or I polypeptide antibody, whereby said A, B, C or D polypeptide or anti-E, F, G, H or I polypeptide antibody binds to said E, F, G, H or I polypeptide, thereby modulating at least one biological activity of said cell, wherein A is a PRO10272 polypeptide, B is a PRO20110 polypeptide, C is a PRO10096 polypeptide, D is a PRO19670 polypeptide, E is a PRO5801 polypeptide, F is a PRO1 polypeptide, G is a PRO20040 polypeptide, H is a PRO20233 polypeptide and I is a PRO1890 polypeptide.

38. The method according to Claim 37, wherein said cell is killed.

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**FIGURE 1**

GGGGCTTCGGCGCCAGCGGCCAGCGCTAGTCGGTCTGGTAAGGATTTACAAAAGGTGCAGGTA  
TGAGCAGGTCTGAAGACTAACATTTTGTGAAGTTGTAAAACAGAAAACCTGTTAGAA**ATGTGG**  
TGGTTTCAGCAAGGCCTCAGTTTCCTTCCTTCAGCCCTTGTAATTTGGACATCTGCTGCTTTC  
ATATTTTCATACATTACTGCAGTAACACTCCACCATATAGACCCGGCTTTACCTTATATCAGT  
GACACTGGTACAGTAGCTCCAGAAAAATGCTTATTTGGGGCAATGCTAAATATTGCGGCAGTT  
TTATGCATTGCTACCATTTATGTTCTGTTATAAGCAAGTTCATGCTCTGAGTCCTGAAGAGAAC  
GTTATCATCAAATTAAACAAGGCTGGCCTTGACTTGGAATACTGAGTTGTTTAGGACTTTCT  
ATTGTGGCAAACCTCCAGAAAACAACCCCTTTTGCTGCACATGTAAGTGGAGCTGTGCTTACC  
TTTGGTATGGGCTCATTATATATGTTTGTTCAGACCATCCTTTCCTACCAAATGCAGCCCAAA  
ATCCATGGCAAACAAGTCTTCTGGATCAGACTGTTGTTGGTTATCTGGTGTGGAGTAAGTGCA  
CTTAGCATGCTGACTTGCTCATCAGTTTTGCACAGTGGCAATTTTGGGACTGATTTAGAACAG  
AAACTCCATTGGAACCCGAGGACAAAGGTTATGTGCTTCACATGATCACTACTGCAGCAGAA  
TGGTCTATGTCATTTTCCTTCTTTGGTTTTTTCCTGACTTACATTCGTGATTTTCAGAAAATT  
TCTTTACGGGTGGAAGCCAATTTACATGGATTAACCCCTCTATGACACTGCACCTTGCCCTATT  
AACAATGAACGAACACGGCTACTTTCAGAGATATTT**TGAT**GAAAGGATAAAATATTTCTGTAA  
TGATTATGATTCTCAGGGATTGGGGAAAGGTTACAGAAGTTGCTTATTCTTCTCTGAAATTT  
TCAACCACTTAATCAAGGCTGACAGTAACACTGATGAATGCTGATAATCAGGAAACATGAAAG  
AAGCCATTTGATAGATTATTCTAAAGGATATCATCAAGAAGACTATTAAAAACACCTATGCCT  
ATACTTTTTTTATCTCAGAAAAATAAGTCAAAAGACTATG

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**FIGURE 2**

<subunit 1 of 1, 266 aa, 1 stop

<MW: 29766, pI: 8.39, NX(S/T): 0

MWWFQQGLSFLPSALVIWTSAAFIIFS YITAVTLHHIDPALPYISDTGTVAPEKCLFGAMLNIA  
AVLCIATYVRYKQVHALSPEENVIIKLNKAGLV LGILSCLGLSIVANFQKTTLFAAHVSGAV  
LTFGMGSLYMFVQTILSYQMOPKIHGKQVFWIRLLLVIWCGVSALSMLTCSSVLHSGNFGTDL  
EQKLHWNPEDKGYVLHMITTAAEWSMSFSF GFFLT YIRDFQKISLRVEANLHGLTLYDTAPC  
PINNERTRLSRDI

**Important features:****Type II transmembrane domain:**

amino acids 13-33

**Other Transmembrane domains:**

amino acids 54-73, 94-113, 160-180, 122-141

**N-myristoylation sites.**

amino acids 57-63, 95-101, 99-105, 124-130, 183-189

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**FIGURE 3**

CGGACGCGTGGGCGGACGCGTGGGGGAGAGCCGAGTCCCGGCTGCAGCACCTGGGAGAAGGC  
AGACCGTGTGAGGGGGCCTGTGGCCCCAGCGTGCTGTGGCCTCGGGGAGTGGGAAGTGGAGGC  
AGGAGCCTTCCTTACACTTCGCCATGAGTTTCCTCATCGACTCCAGCATCATGATTACCTCCC  
AGATACTATTTTTTGGATTTGGGTGGCTTTTCTTCATGCGCCAATTGTTTAAAGACTATGAGA  
TACGTCAGTATGTTGTACAGGTGATCTTCTCCGTGACGTTTGCATTTTCTTGCAACCATGTTTG  
AGCTCATCATCTTTGAAATCTTAGGAGTATTGAATAGCAGCTCCCGTTATTTTCACTGGAAAA  
TGAACCTGTGTGAATTCTGCTGATCCTGGTTTTTCATGGTGCCTTTTTTACATTGGCTATTTTA  
TTGTGAGCAATATCCGACTACTGCATAAACAACGACTGCTTTTTTCTGTCTCTTATGGCTGA  
CCTTTATGTATTTCTTCTGGAACTAGGAGATCCCTTTCCCATTCTCAGCCCCAAACATGGGA  
TCTTATCCATAGAACAGCTCATCAGCCGGGTGGTGTGATTGGAGTGACTCTCATGGCTCTTC  
TTTCTGGATTTGGTGTGTCAACTGCCCATACACTTACATGTCTTACTTCCTCAGGAATGTGA  
CTGACACGGATATTCTAGCCCTGGAACGGCGACTGCTGCAAACCATGGATATGATCATAAGCA  
AAAAGAAAAGGATGGCAATGGCACGGAGAACAATGTTCCAGAAGGGGGGAAGTGCATAACAAAC  
CATCAGGTTTTCTGGGGAATGATAAAAAGTGTTACCACTTCAGCATCAGGAAGTGAAATCTTA  
CTCTTATTCAACAGGAAGTGGATGCTTTGGAAGAATTAAGCAGGCAGCTTTTTCTGGAAACAG  
CTGATCTATATGCTACCAAGGAGAGAATAGAATACTCCAAAACCTTCAAGGGGAAATATTTTA  
ATTTTCTTGGTTACTTTTTCTCTATTTACTGTGTTTGGAAAATTTTCATGGCTACCATCAATA  
TTGTTTTTGATCGAGTTGGGAAAACGGATCCTGTCAAGAGGCATTGAGATCACTGTGAATT  
ATCTGGGAATCCAATTTGATGTGAAGTTTTGGTCCCAACACATTTCTTCATTCTTGTGGAA  
TAATCATCGTCACATCCATCAGAGGATTGCTGATCACTCTTACCAAGTTCTTTTATGCCATCT  
CTAGCAGTAAGTCTCCAATGTCAATTGTCCTGCTATTAGCACAGATAATGGGCATGTACTTTG  
TCTCCTCTGTGCTGCTGATCCGAATGAGTATGCCTTTAGAATACCGCACCATAATCACTGAAG  
TCCTTGAGAACTGCAGTTCAACTTCTATCACCGTTGGTTTGATGTGATCTTCCTGGTCAGCG  
CTCTCTCTAGCATACTCTTCCTCTATTTGGCTCACAAACAGGCACCAGAGAAGCAAATGGCAC  
CTTGAACTTAAGCCTACTACAGACTGTTAGAGGCCAGTGGTTTCAAATTTAGATATAAGAGG  
GGGGAAAAATGGAACCAGGGCCTGACATTTTATAAACAAACAAAATGCTATGGTAGCATTTTTT  
CACCTTCATAGCATACTCCTTCCCCGTCAGGTGATACTATGACCATGAGTAGCATCAGCCAGA  
ACATGAGAGGGAGAACTAACTCAAGACAATACTCAGCAGAGAGCATCCCGTGTGGATATGAGG  
CTGGTGTAGAGGCGGAGAGGCCAAGAACTAAAGGTGAAAAATACACTGGAACCTCTGGGGC  
AAGACATGTCTATGGTAGCTGAGCCAAACACGTAGGATTCCGTTTTAAGGTTACATGGAAA  
AGGTTATAGCTTTGCCTTGAGATTGACTCATTAATAATCAGAGACTGTAACAAAAAAAAAAAAA  
AAAAAAAAGGGCGGCCGCGACTCTAGAGTCGACCTGCAGAAGCTTGGCCGCCATGGCCCAACT  
TGTTTATTGCAGCTTATAATG

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**FIGURE 4**

MSFLIDSSIMITSQILFFGFGWLFEMRQLFKDYEIRQYVVQVIFSVTFAFSCTMFELIIFEIL  
GVLNSSSRYPFHWMNLCVILLILVFMVPFYIGYFIVSNIRLLHKQRLLFSCLLWLTFMYFFWK  
LGDPFPILSPKHGILSIEQLISRVGVIGVTLMALLSGFGAVNCPYTYMSYFLRNVTDTDILAL  
ERRLLQTMDMIISKKKRMAMARRTMFQKGEVHNKPSGFWMIKSVTTSASGSENLTLIQQEVD  
ALEELSRQLFLETADLYATKERIEYSKTFKGKYFNFLGYFFSIYCVWKIFMATINIVFDRVGK  
TDPVTRGIEITVNYLGIQFDVKFWSQHISFILVGIIIVTSIRGLLITLTKFFYAISSSKSSNV  
IVLLLAQIMGYFVSSVLLIRMSMPLEYRTIITEVLGELQFNFYHRWFDVIFLVSALSSILFL  
YLAHKQAPEKQMAP

**Important features:****Signal peptide:**

amino acids 1-23

**Potential transmembrane domains:**amino acids 37-55, 81-102, 150-168, 288-311, 338-356, 375-398,  
425-444**N-glycosylation sites.**

amino acids 67-70, 180-183 and 243-246

**Eukaryotic cobalamin-binding proteins**

amino acids 151-160

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**FIGURE 5**

AGCAGGGAAATCCGGATGTCTCGGTTATGAAGTGGAGCAGTGAGTGTGAGCCTCAACATAGTT  
CCAGAACTCTCCATCCGGACTAGTTATTGAGCATCTGCCTCTCATATCACCAGTGGCCATCTG  
AGGTGTTTTCCCTGGCTCTGAAGGGGTAGGCACG**ATG**GCCAGGTGCTTCAGCCTGGTGTTGCTT  
CTCACTTCCATCTGGACCACGAGGCTCCTGGTCCAAGGCTCTTTGCGTGCAGAAGAGCTTTCC  
ATCCAGGTGTCATGCAGAATTATGGGGATCACCCCTGTGAGCAAAAAGGCGAACCAGCAGCTG  
AATTTACAGAAGCTAAGGAGGCCTGTAGGCTGCTGGGACTAAGTTTGGCCGGCAAGGACCA  
GTTGAAACAGCCTTGAAAGCTAGCTTTGAAACTTGCAGCTATGGCTGGGTGGAGATGGATTCT  
GTGGTCATCTCTAGGATTAGCCCAAACCCCAAGTGTGGGAAAAATGGGGTGGGTGTCCTGATT  
TGGAAGGTTCCAGTGAGCCGACAGTTTGCAGCCTATTGTTACAACCTCATCTGATACTTGGACT  
AACTCGTGCATTCCAGAAATTATCACCACCAAAGATCCCATATTCAACACTCAAACCTGCAACA  
CAAACAACAGAATTTATTGTCAGTGACAGTACCTACTCGGTGGCATCCCCTTACTCTACAATA  
CCTGCCCCTACTACTACTCCTCCTGCTCCAGCTTCCACTTCTATTCCACGGAGAAAAAATTG  
ATTTGTGTACAGAAGTTTTTATGGAAACTAGCACCATGTCTACAGAACTGAACCATTTGTT  
GAAAATAAAGCAGCATTCAAGAATGAAGCTGCTGGGTTTGGAGGTGTCCCCACGGCTCTGCTA  
GTGCTTGCTCTCCTCTTCTTTGGTGCTGCAGCTGGTCTTGGATTTTGCTATGTCAAAGGTAT  
GTGAAGGCCTTCCCTTTTACAAACAAGAATCAGCAGAAGGAAATGATCGAAACCAAAGTAGTA  
AAGGAGGAGAAGGCCAATGATAGCAACCCTAATGAGGAATCAAAGAAAAGTGAATAAAACCCA  
GAAGAGTCCAAGAGTCCAAGCAAAACTACCGTGCGATGCCTGGAAGCTGAAGTT**TAG**ATGAGA  
CAGAAATGAGGAGACACACCTGAGGCTGGTTTTCTTTCATGCTCCTTACCCTGCCCCAGCTGGG  
GAAATCAAAGGGCCAAAGAACCAAAGAAGAAAGTCCACCCTTGGTTTCTTAACCTGGAATCAGC  
TCAGGACTGCCATTGGACTATGGAGTGCACCAAAGAGAATGCCCTTCTCCTTATTGTAACCCT  
GTCTGGATCCTATCCTCCTACCTCCAAAGCTTCCCACGGCCTTCTAGCCTGGCTATGTCTTA  
ATAATATCCCCTGGGAGAAAGGAGTTTTGCAAAGTGCAAGGACCTAAACATCTCATCAGTA  
TCCAGTGGTAAAAAGGCCTCCTGGCTGTCTGAGGCTAGGTGGGTTGAAAGCCAAGGAGTCACT  
GAGACCAAGGCTTTCTCTACTGATTCCGCAGCTCAGACCCTTTCTTCAGCTCTGAAAGAGAAA  
CACGTATCCCACCTGACATGTCCTTCTGAGCCCGGTAAGAGCAAAAGAATGGCAGAAAAGTTT  
AGCCCCTGAAAGCCATGGAGATTCTCATAACTTGAGACCTAATCTCTGTAAAGCTAAAATAAA  
GAAATAGAACAAGGCTGAGGATACGACAGTACACTGTCAGCAGGGACTGTAAACACAGACAGG  
GTCAAAGTGTTTTCTCTGAACACATTGAGTTGGAATCACTGTTTGAACACACACACTTACTT  
TTTCTGGTCTCTACCACTGCTGATATTTTCTCTAGGAAATATACTTTTACAAGTAACAAAAAT  
AAAAACTCTTATAAATTTCTATTTTTATCTGAGTTACAGAAATGATTACTAAGGAAGATTACT  
CAGTAATTTGTTTTAAAAAGTAATAAAATTCAACAAACATTTGCTGAATAGCTACTATATGTCA  
AGTGCTGTGCAAGGTATTACACTCTGTAATTGAATATTATTCCTCAAAAAATTGCACATAGTA  
GAACGCTATCTGGGAAGCTATTTTTTTTTCAGTTTTGATATTTCTAGCTTATCTACTTCCAACT  
AATTTTTATTTTTGCTGAGACTAATCTTATTCATTTTCTCTAATATGGCAACCATTATAACCT  
TAATTTATTATTAAACATACCTAAGAAGTACATTGTTACCTCTATATAACCAAGCACATTTTAA  
AAGTGCCATTAACAAATGTATCACTAGCCCTCCTTTTTTCCAACAAGAAGGGACTGAGAGATGC  
AGAAATATTTGTGACAAAAAATTAAAGCATTTAGAAACTT

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**FIGURE 6**

MARCFSLVLLLLTSIWTTTRLLVQGSLRAEELSIQVSCRIMGITLVSKKANQQLNFTAKEACRL  
LGLSLAGKDQVETALKASFETCSYGWVGDFVVISRISPNPKCGKNGVGVLIWKVPVSRQFAA  
YCYNSSDTWTNSCIPEIITTKDPIFNTQTATQTTEFIVSDSTYSVASPYSTIPAPTTTPPAPA  
STSIPRRKKLICVTEVFMETSTMSTETEPFVENKAAFKNEAAGFGGVPTALLVLALLFFGAAA  
GLGFCYVKRYVKAFPFTNKNQQKEMIETKVVKEEKANDSNPNEESKKTDKNPPEESKSPSKTTV  
RCLEAEV

**Signal sequence:**

amino acids 1-16

**Transmembrane domain:**

amino acids 235-254

**N-glycosylation site.**

amino acids 53-57, 130-134, 289-293

**Casein kinase II phosphorylation site.**

amino acids 145-149, 214-218

**Tyrosine kinase phosphorylation site.**

amino acids 79-88

**N-myristoylation site.**

amino acids 23-29, 65-71, 234-240, 235-239, 249-255, 253-259



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**FIGURE 7**

CGCCGCGCTCCCGCACCCGCGGCCCCGCCACCGCGCCGCTCCCGCATCTGCACCCGCGAGCCCG  
GCGGCCCTCCCGGCGGGAGCGAGCAGATCCAGTCCGGCCCCGAGCGCAACTCGGTCCAGTCGGG  
GCGGCGGCTGCGGGCGCAGAGCGGAGATGAGCGGCTTGGGGCCACCCTGCTGTGCCTGCTGC  
TGGCGGCGGCGGTCCCCACGGCCCCCGCGCCGCTCCGACGGCGACCTCGGCTCCAGTCAAGC  
CCGGCCCCGGCTCTCAGCTACCCGCGAGGAGGAGGCCACCCTCAATGAGATGTTCCGCGAGGTTG  
AGGAAGTGTGAGGACACGCAGCACAATTGCGCAGCGCGGTGGAAGAGATGGAGGCAGAAG  
AAGCTGCTGCTAAAGCATCATCAGAAAGTGAACCTGGCAAACCTTACCTCCCAGCTATCACAATG  
AGACCAACACAGACACGAAGGTTGGAAATAATACCATCCATGTGCACCGAGAAATTCACAAGA  
TAACCAACAACCAGACTGGACAAATGGTCTTTTCAGAGACAGTTATCACATCTGTGGGAGACG  
AAGAAGGCAGAAGGAGCCACGAGTGCATCATCGACGAGGACTGTGGGCCAGCATGTACTGCC  
AGTTTGCCAGCTTCCAGTACACCTGCCAGCCATGCCGGGGCCAGAGGATGCTCTGCACCCGGG  
ACAGTGAGTGTGTGGAGACCAGCTGTGTGTCTGGGGTCACTGCACCAAATGGCCACCAGGG  
GCAGCAATGGGACCATCTGTGACAACCAGAGGGACTGCCAGCCGGGGCTGTGCTGTGCCTTCC  
AGAGAGGCCTGCTGTTCCCTGTGTGCACACCCCTGCCCGTGGAGGGCGAGCTTTGCCATGACC  
CCGCCAGCCGGCTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGGACCGAT  
GCCCTTGTGCCAGTGGCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTGTGCAAGC  
CGACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCAGAGAGGTCCCCGATG  
AGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGAGAGGAGCC  
TGACTGAAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCCGCGCTGCACTGCTGGGAGGGGAAG  
AGATTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAATAGCTAATTTATTTCCCA  
GGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCTACATCTTCTTCCAGTAAGTTTCC  
CCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTTCACTCCCCAGGCTGTTCTCCAGGC  
TTCACAGTCTGGTGTCTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTTGCCACCCCT  
GTCCAGATTATTGGCTGCTTTGCCCTCTACCAAGTTGGCAGACAGCCGTTTGTCTACATGGCTT  
TGATAATTGTTTGGGGGAGGAGATGGAACAATGTGGAGTCTCCCTCTGATTGGTTTTGGGG  
AAATGTGGAGAAGAGTGCCCTGCTTTGCAACATCAACCTGGCAAAAATGCAACAAATGAATT  
TTCCACGCAGTTCTTTCCATGGGCATAGGTAAGCTGTGCCTTCAGCTGTTGCAGATGAAATGT  
TCTGTTACCCCTGCATTACATGTGTTTATTCATCCAGCAGTGTGCTCAGCTCCTACCTCTGT  
GCCAGGGCAGCATTTTCATATCCAAGATCAATTCCCTCTCTCAGCACAGCCTGGGGAGGGGGT  
CATTGTTCTCCTCGTCCATCAGGGATCTCAGAGGCTCAGAGACTGCAAGCTGCTTGCCCAAGT  
CACACAGCTAGTGAAGACCAGAGCAGTTTCATCTGGTTGTGACTCTAAGCTCAGTGCTCTCTC  
CACTACCCACACAGCCTTGGTGCCACCAAAAAGTGCTCCCCAAAAGGAAGGAGAATGGGATT  
TTTCTTGAGGCATGCACATCTGGAATTAAGGTCAAACCTAATTCTCACATCCCTCTAAAAGTAA  
ACTACTGTTAGGAACAGCAGTGTCTCACAGTGTGGGGCAGCCGTCCTTCTAATGAAGACAAT  
GATATTGACACTGTCCCTCTTTGGCAGTTGCATTAGTAACCTTGAAAGGTATATGACTGAGCG  
TAGCATACAGGTTAACCTGCAGAAACAGTACTTAGGTAATTGTAGGGCGAGGATTATAAATGA  
AATTTGCAAAATCACTTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACC  
GAGCAGGGCTGTGTGAAACATGGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCACTC  
CACAAATGATGTTTTAGGTGTCATGGACTGTTGCCACCATGTATTCATCCAGAGTTCTTAA  
GTTTAAAGTTGCACATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATGTATAACAT  
AAGTTGCATTTAGAAATCAAGCATAAATCACTTCAACTGCAAAAAAAAAAAAAAAAAAAAAA  
AAA

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**FIGURE 8**

MQRLGATLLCLLLAAAVPTAPAPAPTATSAPVKPGPALSYPQEEATLNEMFREVEELMEDTQH  
KLRS AVEEMEAEEAAAKASSEVNLANLPPSYHNETNTDTKVGNN TIHVHREIHKITNNQTGQM  
VFSETVITSVGDEEGRRSHECIIDEDCGPSMYCQFASFQYTCQPCRGQRM LCTR DSECCGDQL  
CVWGHCTKMATRGSNGTICDNQRDCQ PGLCCA FQRGLLFPVCTPLPVEGELCHDPASRLLDLI  
TWELEPDGALDRCPCASGLLCQPHSHSLVYVCKPTFVGSRDQDGEILLPREVPDEYEVGSFME  
EVRQELEDLERSLTEEMALGEPAAAAAALLGGEI

**Signal sequence:**

amino acids 1-19

**N-glycosylation site.**

amino acids 96-100, 106-110, 121-125, 204-208

**Casein kinase II phosphorylation site.**amino acids 46-50, 67-71, 98-102, 135-139, 206-210, 312-316,  
327-331**N-myristoylation site.**

amino acids 202-208, 217-223

**Amidation site.**

amino acids 140-144

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**FIGURE 9**

**CGG**ACGCGTGGGCGGACGCGTGGGGGCTGTGAGAAAGTGCCAATAAATACATCATGCAACCCC  
ACGGCCACCTTGTGAACTCCTCGTGCCAGGGCTGATGTGCGTCTTCCAGGGCTACTCATCC  
AAAGGCCTAATCCAACGTTCTGTCTTCAATCTGCAAATCTATGGGGTCTTGGGGCTCTTCTGG  
ACCCTTAACTGGGTACTGGCCCTGGGCCAATGCGTCCTCGCTGGAGCCTTTGCCTCCTTCTAC  
TGGGCCTTCCACAAGCCCCAGGACATCCCTACCTTCCCTTAATCTCTGCCTTCATCCGCACA  
CTCCGTTACCACACTGGGTCAATTGGCATTGAGGCCCTCATCCTGACCCTTGTGCAGATAGCC  
CGGGTCATCTTGGAGTATATTGACCACAAGCTCAGAGGAGTGAGAACCTGTAGCCCGCTGC  
ATCATGTGCTGTTTCAAGTGCTGCCTCTGGTGTCTGGAAAAATTTATCAAGTTCCTAAACCGC  
AATGCATACATCATGATCGCCATCTACGGGAAGAATTTCTGTGTCTCAGCCAAAAATGCGTTC  
ATGCTACTCATGCGAAACATTGTCAGGGTGGTCTGCTGGACAAAGTCACAGACCTGCTGCTG  
TTCTTTGGGAAGCTGCTGGTGGTCGGAGGCGTGGGGGTCTGTCTTCTTTTCTCCGGT  
CGCATCCCGGGGCTGGGTAAAGACTTTAAGAGCCCCACCTCACTATTACTGGCTGCCCATC  
ATGACCTCCATCCTGGGGGCTATGTCATCGCCAGCGGCTTCTTCAGCGTTTTTCGGCATGTGT  
GTGGACACGCTCTTCTCTGCTTCCTGGAAGACCTGGAGCGGAACAACGGCTCCCTGGACCGG  
CCCTACTACATGTCCAAGAGCCTTCTAAAGATTCTGGGCAAGAAGAACGAGGCGCCCCCGGAC  
AACAAGAAGAGGAAGAAG**TGA**CAGCTCCGGCCCTGATCCAGGACTGCACCCACCCCCACCGT  
CCAGCCATCCAACCTCACTTCGCCTTACAGGTCTCCATTTTGTGGTAAAAAAGGTTTTAGGC  
CAGGCGCCGTGGCTCACGCCTGTAATCCAACACTTTGAGAGGCTGAGGCGGGCGGATCACCTG  
AGTCAGGAGTTCGAGACCAGCCTGGCCAACATGGTGAAACCTCCGTCTCTATTAAAAATACAA  
AAATTAGCCGAGAGTGGTGGCATGCACCTGTCATCCCAGCTACTCGGGAGGCTGAGGCAGGAG  
AATCGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGCCGAGATCGCGCCACTGCACTCCAACC  
TGGGTGACAGACTCTGTCTCCAAAACAAAACAAACAAAAGATTTTATTAAAGATATTT  
TGTTAACTC

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**FIGURE 10**

RTRGRTRGGCEKVPINTSCNPTAHLVNSSCPGLMCVFQGYSSKGLIQRSVFNLQIYGVLGLFW  
TLNWVLALGQCVLGAFASFYWAFHKPQDIPTFPLISAFIRTLRYHTGSLAFGALILTLVQIA  
RVILEYIDHKLRGVQNPVARCIMCCFKCCLWCLEKFIKFLNRNAYIMIAIYGKNFCVSAKNAF  
MLLMRNIVRVVLDKVTDLLLFFGKLLVVGGVGVLSFFFFSGRIPGLGKDFKSPHLNYYWLPI  
MTSILGAYVIASGFFSVFGMCVDTLFLCFLEDLERNNGSLDRPYMSKSLKILGKKNEAPPD  
NKKRKK

**Important features:****Transmembrane domains:**

amino acids 57-80 (type II), 110-126, 215-231, 254-274

**N-glycosylation sites.**

amino acids 16-20, 27-31, 289-293

**Hypothetical YBR002c family proteins.**

amino acids 276-288

**Ammonium transporters proteins.**

amino acids 204-231

**N-myristoylation sites.**

amino acids 60-66, 78-84

**Amidation site.**

amino acids 306-310

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**FIGURE 11**

GCCCCGCGCCCGGCGCCGGGCGCCCCGAAGCCGGGAGCCACCGCCATGGGGGCCTGCCTGGGAG  
CCTGCTCCCTGCTCAGCTGCGCGTCCTGCCTCTGCGGCTCTGCCCCCTGCATCCTGTGCAGCT  
GCTGCCCCGCCAGCCGCAACTCCACCGTGAGCCGCTCATCTTCACGTTCTTCTCTTCTG  
GGGTGCTGGTGTCCATCATTATGCTGAGCCCGGGCGTGGAGAGTCAGCTCTACAAGCTGCCCT  
GGGTGTGTGAGGAGGGGGCCGGGATCCCCACCGTCCTGCAGGGCCACATCGACTGTGGCTCCC  
TGCTTGGCTACCGCGCTGTCTACCGCATGTGCTTCGCCACGGCGGCCTTCTTCTTCTTCTTT  
TCACCCTGCTCATGCTCTGCGTGAGCAGCAGCCGGGACCCCCGGGCTGCCATCCAGAATGGGT  
TTTGGTTCTTTAAGTTCCTGATCCTGGTGGGCCTCACCGTGGGTGCCTTCTACATCCCTGACG  
GCTCCTTCACCAACATCTGGTTCTACTTCGGCGTCGTGGGCTCCTTCTTCTTCATCCTCATCC  
AGCTGGTGCTGCTCATCGACTTTGCGCACTCCTGGAACCAGCGGTGGCTGGGCAAGGCCGAGG  
AGTGCGATTCCCCTGCCTGGTACGCAGGCCTCTTCTTCTTCACTCTCCTCTTCTACTTGCTGT  
CGATCGCGGCCGTGGCGCTGATGTTTATGTACTACACTGAGCCAGCGGCTGCCACGAGGGCA  
AGGTCTTCATCAGCCTCAACCTCACCTTCTGTGTCTGCGTGTCCATCGCTGCTGTCTGCCCCA  
AGGTCCAGGACGCCCAGCCCAACTCGGGTCTGCTGCAGGCCTCGGTTCATCACCCTCTACACCA  
TGTTTGTACCTGGTCAGCCCTATCCAGTATCCCTGAACAGAAATGCAACCCCCATTTGCCAA  
CCCAGCTGGGCAACGAGACAGTTGTGGCAGGCCCCGAGGGCTATGAGACCCAGTGGTGGGATG  
CCCCGAGCATTGTGGGCCTCATCATCTTCTCCTGTGCACCCTCTTCATCAGTCTGCGCTCCT  
CAGACCACCGGCAGGTGAACAGCCTGATGCAGACCGAGGAGTGCCACCTATGCTAGACGCCA  
CACAGCAGCAGCAGCAGCAGGTGGCAGCCTGTGAGGGCCGGGCCTTTGACAACGAGCAGGACG  
GCGTCACCTACAGCTACTCCTTCTTCCACTTCTGCCTGGTGTGGCCTCACTGCACGTCATGA  
TGACGCTCACCAACTGGTACAAGCCCGGTGAGACCCGGAAGATGATCAGCAGTGGACCGCCG  
TGTGGGTGAAGATCTGTGCCAGCTGGGCAGGGCTGCTCCTCTACCTGTGGACCCTGGTAGCCC  
CACTCCTCCTGCGCAACCGCGACTTCAGCTTGAGGCAGCCTCACAGCCTGCCATCTGGTGCCTC  
CTGCCACCTGGTGCCTCTCGGCTCGGTGACAGCCAACCTGCCCCCTCCCCACACCAATCAGCC  
AGGCTGAGCCCCCACCCTGCCCCAGCTCCAGGACCTGCCCCCTGAGCCGGGCCTTCTAGTCGT  
AGTGCCTTCAGGGTCCGAGGAGCATCAGGCTCCTGCAGAGCCCCATCCCCCGCCACACCCAC  
ACGGTGGAGCTGCCTCTTCTTCCCCCTCCTCCCTGTTGCCATACTCAGCATCTCGGATGAAA  
GGGCTCCCTTGTCTCAGGCTCCACGGGAGCGGGGCTGCTGGAGAGAGCGGGGAACCTCCCACC  
ACAGTGGGGCATCCGGCACTGAAGCCCTGGTGTTCCTGGTCACGTCCCCCAGGGGACCCTGCC  
CCCTTCTGACTTCGTGCCTTACTGAGTCTCTAAGACTTTTTCTAATAAACAAGCCAGTGCG  
TGTAATAAAAAA

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**FIGURE 12**

MGACLGACSLSCASCLCGSAPCILCSCCPASRNSTVSRLLFTFFLFLGVLVSIIMLSPGVES  
QLYKLPWVCEEAGIPTVLQGHIDCGSLLGYRAVYRMCFATAAFFFFFFFFTLLMLCVSSSRDPR  
AAIQNGFWFFKFLILVGLTVGAFYIPDGSEFTNIWFYFGVVGSFLFILIQLVLLIDFAHSWNQR  
WLGKAEECDSRAWYAGLFFFTLLFYLLSIAAVALMFMYYTEPSGCHEGKVFISLNLTFVCVVS  
IAAVLPKVQDAQPNSGLLQASVITLYTMFVTWSALSSIPEQKCNPHLPTQLGNETVVAGPEGY  
ETQWWDAPSIVGLIIFLLCTLFISLRSSDHRQVNSLMQTEECPPMLDATQQQQQQVAACEGRA  
FDNEQDGVITYSYFFHFCLVLASLHVMMTLTNWYKPGETRMISTWTAVVWKICASWAGLLLY  
LWTLVAPLLLNRDFS

**Signal sequence:**

amino acids 1-20

**Transmembrane domains:**

amino acids 40-58, 101-116, 134-150, 162-178, 206-223, 240-257,  
272-283, 324-340, 391-406, 428-444

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**FIGURE 13**

CGGGCCAGCCTGGGGCGGCCGGCCAGGAACCAACCCGTTAAGGTGTCTTCTCTTTAGGGATGGT  
GAGGTTGGAAAAAGACTCCTGTAACCCCTCCTCCAGGATGAACCACCTGCCAGAAGACATGGAG  
AACGCTCTCACCGGGAGCCAGAGCTCCCATGCTTCTCTGCGCAATATCCATTCCATCAACCCC  
ACACAACTCATGGCCAGGATTGAGTCCTATGAAGGAAGGGAAAAAGAAAGGCATATCTGATGTC  
AGGAGGACTTTCTGTTTGTGTTGTCACCTTTGACCTCTTATTTCGTAACATTACTGTGGATAATA  
GAGTTAAATGTGAATGGAGGCATTGAGAACACATTAGAGAAGGAGGTGATGCAGTATGACTAC  
TATTCTTCATATTTTGATATATTTCTTCTGGCAGTTTTTCGATTAAAGTGTTAATACTTGCA  
TATGCTGTGTGCAGACTGCGCCATTGGTGGGCAATAGCGTTGACAACGGCAGTGACCAGTGCC  
TTTTTACTAGCAAAAGTGATCCTTTCGAAGCTTTTCTCTCAAGGGGCTTTTGGCTATGTGCTG  
CCCATCATTTTCATTCATCCTTGCCCTGGATTGAGACGTGGTTCCTGGATTTCAAAGTGTTACCT  
CAAGAAGCAGAAGAAGAAAACAGACTCCTGATAGTTTCAGGATGCTTCAGAGAGGGCAGCACTT  
ATACCTGGTGGTCTTTCTGATGGTCAGTTTTATTCCCCTCCTGAATCCGAAGCAGGATCTGAA  
GAAGCTGAAGAAAAACAGGACAGTGAGAAACCACTTTTAGAACTATAGACTACTTTTTGTGA  
AATGTGAAAAACCCTCACAGAAAGTCATCGAGGCAAAAAGAGGCAGGCAGTGGAGTCTCCCTG  
TCGACAGTAAAGTTGAAATGGTGACGTCCACTGCTGGCTTTATTGAACAGCTAATAAAGATTT  
ATTTATTGTAATACCTCACAAACGTTGTACCATATCCATGCACATTTAGTTGCCTGCCTGTGG  
CTGGTAAGGTAATGTCATGATTCATCCTCTCTTCAGTGAGACTGAGCCTGATGTGTGAACAAA  
TAGGTGAAGAAAGTCTTGTGCTGTATTCCTAATCAAAGACTTAATATATTGAAGTAACACTT  
TTTTAGTAAGCAAGATACCTTTTTTATTTCAATTCACAGAATGGAATTTTTTTGTTTCATGTCT  
CAGATTTATTTTGTATTTCTTTTTTAACACTCTACATTTCCCTTGTTTTTTAACTCATGCACA  
TGTGCTCTTTGTACAGTTTTTAAAAAGTGTAATAAAATCTGACATGTCAATGTGGCTAGTTTTTA  
TTTTTCTTGTTTTGCATTATGTGTATGGCCTGAAGTGTTGGACTTGCAAAAGGGGAAGAAAGG  
AATTGCGAATACATGTAAAATGTCACCAGACATTTGTATTATTTTTATCATGAAATCATGTTT  
TTCTCTGATTGTTCTGAAATGTTCTAAATACTCTTATTTTGAATGCACAAAATGACTTAAACC  
ATTCATATCATGTTTCCTTTGCGTTTCAGCCAATTTCAATTAAAATGAACTAAATTAAAAA

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**FIGURE 14**

MNHLPEDMENALTGSQSSHASLRNIHSINPTQLMARIESYEGREKKGISDVRRTFCLFVTFDL  
LFVTLLWIIELNVNGGIEN'TLEKEVMQYDYSSYFDIFLLAVFRFKVLILAYAVCRLRHWWAI  
ALTTAVTSAFLLAKVILSKLFSQGAFGYVLPPIISFILAWIETWFLDFKVLQPQEAEEENRLLIV  
QDASERAALIPGGLSDGQFYSPPESEAGSEEAEEKQDSEKPLEL

**Important features of the protein:****Signal peptide:**

amino acids 1-20

**Transmembrane domains:**

amino acids 54-72, 100-118, 130-144, 146-166

**N-myristoylation sites.**

amino acids 14-20, 78-84, 79-85, 202-208, 217-223



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**FIGURE 15**

ACTCGAACGCAGTTGCTTCGGGACCCAGGACCCCCTCGGGCCCCGACCCGCCAGGAAAGACTGA  
GGCCGCGGCCTGCCCCGCCCCGGCTCCCTGCGCCGCCGCCCTCCCGGGACAGAAG**ATG**TGCT  
CCAGGGTCCCTCTGCTGCTGCCGCTGCTCCTGCTACTGGCCCTGGGGCTGGGGTGCAGGGCT  
GCCCATCCGGCTGCCAGTGCAGCCAGCCACAGACAGTCTTCTGCACTGCCCCGCCAGGGGACCA  
CGGTGCCCCGAGACGTGCCACCCGACACGGTGGGGCTGTACGTCTTTGAGAACGGCATCACCA  
TGCTCGACGCAGGCAGCTTTGCCGGCCTGCCGGGCTGCAGCTCCTGGACCTGTACAGAAACC  
AGATCGCCAGCCTGCCCAGCGGGGTCTTCCAGCCACTCGCCAACCTCAGCAACCTGGACCTGA  
CGGCCAACAGGCTGCATGAAATCACCAATGAGACCTTCCGTGGCCTGCGGGCCTCGAGCGCC  
TCTACCTGGGCAAGAACCGCATCCGCCACATCCAGCCTGGTGCCTTCGACACGCTCGACCGCC  
TCCTGGAGCTCAAGCTGCAGGACAACGAGCTGCGGGCACTGCCCCCGCTGCGCCTGCCCCGCC  
TGCTGCTGCTGGACCTCAGCCACAACAGCCTCCTGGCCCTGGAGCCCGGCATCCTGGACACTG  
CCAACCTGGAGGCGCTGCGGCTGGCTGGTCTGGGGCTGCAGCAGCTGGACGAGGGGCTCTTCA  
GCCGCTTGCGCAACCTCCACGACCTGGATGTGTCCGACAACCAGCTGGAGCGAGTGCCACCTG  
TGATCCGAGGCCTCCGGGGCCTGACGCGCCTGCGGCTGGCCGGCAACACCCGCATTGCCCAGC  
TGCGGGCCCGAGGACCTGGCCGGCCTGGCTGCCCTGCAGGAGCTGGATGTGAGCAACCTAAGCC  
TGCAGGCCCTGCCTGGCGACCTCTCGGGCCTCTTCCCCCGCCTGCGGCTGCTGGCAGCTGCC  
GCAACCCCTTCAACTGCGTGTGCCCCCTGAGCTGGTTTGGCCCTGGGTGCGCGAGAGCCACG  
TCACACTGGCCAGCCCTGAGGAGACGCGCTGCCACTTCCCGCCCAAGAAGCTGGCCGGCTGC  
TCCTGGAGCTTGACTACGCCGACTTTGGCTGCCCAGCCACCACCACACAGCCACAGTGCCCA  
CCACGAGGCCCCGTGGTGCGGGAGCCACAGCCTTGTCTTCTAGCTTGGCTCCTACCTGGCTTA  
GCCCCACAGCGCCGGCCACTGAGGCCCCCAGCCCGCCCTCCACTGCCCCACCGACTGTAGGGC  
CTGTCCCCCAGCCCCAGGACTGCCACCCGTCCACCTGCCTCAATGGGGGACATGCCACCTGG  
GGACACGGCACCACCTGGCGTGTGTCGCCCCGAGGCTTACGGGCTGTACTGTGAGAGCC  
AGATGGGGCAGGGGACAGGCCACCCCTACACCAGTACGCGGAGGCCACCACGGTCCCTGA  
CCCTGGGCATCGAGCCGGTGAGCCCCACCTCCCTGCGCGTGGGGCTGCAGCGCTACCTCCAGG  
GGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTATCGCAACCTATCGGGCCCTGATAAGC  
GGCTGGTGACGCTGCGACTGCCTGCCTCGCTCGCTGAGTACACGGTCACCCAGCTGCGGCCCA  
ACGCCACTTACTCCGTCTGTGTCATGCCTTTGGGGCCCGGGCGGGTGCCGGAGGGCGAGGAGG  
CCTGCGGGGAGGCCCCATACACCCCCAGCCGTCCACTCCAACCACGCCCCAGTCACCCAGGCCC  
GCGAGGGCAACCTGCCGCTCCTCATTGCGCCCCGCCCTGGCCGCGGTGCTCCTGGCCGCGCTGG  
CTGCGGTGGGGGCAGCCTACTGTGTGCGGCGGGGGCGGGCCATGGCAGCAGCGGCTCAGGACA  
AAGGGCAGGTGGGGCCAGGGGCTGGGCCCCCTGGAAGTGGAGGGAGTGAAGGTCCCTTGGAGC  
CAGGCCCCAAGGCAACAGAGGGCGGTGGAGAGGCCCTGCCAGCGGTCTGAGTGTGAGGTGC  
CACTCATGGGCTTCCCAGGGCCTGGCCTCCAGTCACCCCTCCACGCAAAGCCCTACATC**TAA**G  
CCAGAGAGAGACAGGGCAGCTGGGGCCGGGCTCTCAGCCAGTGAGATGGCCAGCCCCCTCCTG  
CTGCCACACCACGTAAGTTCTCAGTCCCAACCTCGGGGATGTGTGCAGACAGGGCTGTGTGAC  
CACAGCTGGGCCCTGTTCCCTCTGGACCTCGGTCTCCTCATCTGTGAGATGCTGTGGCCAGC  
TGACGAGCCCTAACGTCCCCAGAACCAGTGCCTATGAGGACAGTGTCCGCCCTGCCCTCCGC  
AACGTGCAGTCCCTGGGCACGGCGGGCCCTGCCATGTGCTGGTAACGCATGCCTGGGTCTGC  
TGGGCTCTCCCACTCCAGGCGGACCCTGGGGGCCAGTGAAGGAAGCTCCCGGAAAGAGCAGAG  
GGAGAGCGGGTAGGCGGCTGTGTGACTCTAGTCTTGGCCCCAGGAAGCGAAGGAACAAAAGAA  
ACTGGAAGGAAGATGCTTTAGGAACATGTTTTGCTTTTTTAAATATATATATTATTAAGAG  
ATCCTTTCCCATTTATTCTGGGAAGATGTTTTCAAACCTCAGAGACAAGGACTTTGGTTTTTG  
TAAGACAAACGATGATATGAAGGCCTTTTGTAAAGAAAAATAAAAGATGAAGTGTGAAA

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**FIGURE 16**

MCSRVPLLLLPLLLLLLALGPGVQGCPSGCQCSQPQTVFCTARQGTTPRDPVPPDTVGLYVFENG  
ITMLDAGSFAGLPGLQLLDLSQNQIASLPSGVFQPLANLSNLDLTANRLHEITNETFRGLRRL  
ERLYLGKNRIRHIQPGAFDTLDRLLELKLQDNELRALPPLRLPRLLLLDLSHNSLLALEPGIL  
DTANVEALRLAGLGLQQLDEGLFSRLRNLDLDVSDNQLERVPPVIRGLRGLTRLRLAGNTRI  
AQLRPEDLAGLAALQELDVSNSLQALPGDLSGLFPRLRLAAARNPFNCVCPLSWFGPWVRE  
SHVTLASPEETRCHFPKPNAGRLLLELDYADFGCPATTTTATVPTRPVVREPTALSSSLAPT  
WLSPTAPATEAPSPSTAPPTVGPVPQPDCCPSTCLNGGTCHLGRHHLACLCPEGFTGLYC  
ESQMGGQTRPSPTPVTPRPPRSLTGIEPVSPSTSLRVGLQRYLQGSSVQLRSLRLTYRNLSP  
DKRLVTLRPLASLAEYTVTQLRPNATYSVCVMPLGPGRVPEGEEACGEAHTPPAVHSNHAPVT  
QAREGNPLLIAPALAAVLLAALAAGVGAAYCVRGRAMAAAAQDKGVGPGAGPLELEGVKVP  
LEPGPKATEGGGEALPSGSECEVPLMGFPGLQSPLHAKPYI

**Important features:****Signal peptide:**

amino acids 1-23

**Transmembrane domain:**

amino acids 579-599

**EGF-like domain cysteine pattern signature.**

amino acids 430-442

**Leucine zipper pattern.**

amino acids 197-219, 269-291

**N-glycosylation sites.**

amino acids 101-105, 117-121, 273-277, 500-504, 528-532

**Tyrosine kinase phosphorylation sites.**

amino acids 124-131, 337-345

**N-myristoylation sites.**amino acids 23-29, 27-33, 70-76, 142-148, 187-193, 348-354,  
594-600, 640-646

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**FIGURE 17**

GCAGCGGCGAGGCGGCGGTGGTGGCTGAGTCCGTGGTGGCAGAGGCGAAGGCGACAGCTC**ATG**  
CGGGTCCGGATAGGGCTGACGCTGCTGCTGTGTGCGGTGCTGCTGAGCTTGGCCTCGGCGTCC  
TCGGATGAAGAAGGCAGCCAGGATGAATCCTTAGATTCCAAGACTACTTTGACATCAGATGAG  
TCAGTAAAGGACCATACTACTGCAGGCAGAGTAGTTGCTGGTCAAATATTTCTTGATTCAGAA  
GAATCTGAATTAGAATCCTCTATTCAAGAAGAGGAAGACAGCCTCAAGAGCCAAGAGGGGGAA  
AGTGTCACAGAAGATATCAGCTTTCTAGAGTCTCCAAATCCAGAAAACAAGGACTATGAAGAG  
CCAAAGAAAGTACGGAAACCAGCTTTGACCGCCATTGAAGGCACAGCACATGGGGAGCCCTGC  
CACTTCCCTTTTCTTTTCCTAGATAAGGAGTATGATGAATGTACATCAGATGGGAGGGAAGAT  
GGCAGACTGTGGTGTGCTACAACCTATGACTACAAAGCAGATGAAAAGTGGGGCTTTTGTGAA  
ACTGAAGAAGAGGCTGCTAAGAGACGGCAGATGCAGGAAGCAGAAATGATGTATCAAACCTGGA  
ATGAAAATCCTTAATGGAAGCAATAAGAAAAGCCAAAAAGAGAAGCATATCGGTATCTCCAA  
AAGGCAGCAAGCATGAACCATAACCAAGCCCTGGAGAGAGTGTGATATGCTCTTTTATTTGGT  
GATTACTTGCCACAGAATATCCAGGCAGCGAGAGAGATGTTTGAGAAGCTGACTGAGGAAGGC  
TCTCCCAAGGGACAGACTGCTCTTGGCTTTCTGTATGCCTCTGGACTTGGTGTTAATTCAGT  
CAGGCAAAGGCTCTTGATATATTATACATTTGGAGCTCTTGGGGGCAATCTAATAGCCCACATG  
GTTTGGTAAGTAGACTTT**TAG**TGGAAGGCTAATAATATTAACATCAGAAGAATTTGTGGTTTA  
TAGCGGCCACAACTTTTTCAGCTTTCATGATCCAGATTTGCTTGTATTAAGACCAAATATTCA  
GTTGAACCTCCTTCAAATTCCTTGTTAATGGATATAACACATGGAATCTACATGTAAATGAAAG  
TTGGTGGAGTCCACAATTTTTCTTTAAATGATTAGTTTGGCTGATTGCCCCTAAAAAGAGAG  
ATCTGATAAATGGCTCTTTTTAAATTTTCTCTGAGTTGGAATTGTCAGAATCATTTTTTACAT  
TAGATTATCATAATTTTAAAAATTTTCTTTAGTTTTCAAAATTTTGTAATGGTGGCTATA  
GAAAAACAACATGAAATATTATACAATTTTTGCAACAATGCCCTAAGAATTGTTAAATTTCA  
TGGAGTTATTTGTGCAGAATGACTCCAGAGAGCTCTACTTTCTGTTTTTTACTTTTCATGATT  
GGCTGTCTTCCCATTTATTCTGGTCATTTATTGCTAGTGACACTGTGCCTGCTTCCAGTAGTC  
TCATTTTCCCTATTTTGCTAATTTGTTACTTTTTCTTTGCTAATTTGGAAGATTAACATCATTT  
TTAATAAAATTATGTCTAAGATTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 18**

MRVRIGLTLLLCVLLSLASASSDEEGSQDESILDSKTTLTSDSVKDHTTAGRVVAGQIFLDS  
EESSELESSIQEEEDSLKSQEGESVTEDISFLESPNPENKDYEEPKKVRKPALTAIEGTAHGEP  
CHFPFLFLDKEYDECTSDGREDGRLWCATTYDYKADEKWGFCETEEEEAAKRRQMQEAEEMMYQT  
GMKILNGSNKKSQKREAYRYLQKAASMNHTKALERSYALLFGDYLPQNIQAAREMFEEKLTEE  
GSPKGQTALGFLYASGLGVNSSQAKALVYYTFGALGGNLIAMVLSRL

**Important features:****Signal peptide:**

amino acids 1-21

**N-glycosylation sites.**

amino acids 195-199, 217-221, 272-276

**Tyrosine kinase phosphorylation site.**

amino acids 220-228

**N-myristoylation sites.**

amino acids 120-126, 253-259, 268-274, 270-274, 285-291, 289-295

**Glycosaminoglycan attachment site.**

amino acids 267-271

**Microbodies C-terminal targeting signal.**

amino acids 299-303

**Type II fibronectin collagen-binding domain protein.**

amino acids 127-169

**Fructose-bisphosphate aldolase class-II protein.**

amino acids 101-119

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**FIGURE 19**

AATTCAGATTTTAAAGCCCATCTGCAGTGGAATTTTCATGAACTAGCAAGAGGACACCATCTTC  
TTGTATTATACAAGAAAGGAGTGACCTATCACACACAGGGGGAAAAATGCTCTTTTGGGTGC  
TAGGCCTCCTAATCCTCTGTGGTTTTCTGTGGACTCGTAAAGGAAAACCTAAAGATTGAAGACA  
TCACTGATAAGTACATTTTTATCACTGGATGTGACTCGGGCTTTGGAAACTTGGCAGCCAGAA  
CTTTTGATAAAAAGGGATTTTCATGTAATCGCTGCCTGTCTGACTGAATCAGGATCAACAGCTT  
TAAAGGCAGAAACCTCAGAGAGACTTCGTACTGTGCTTCTGGATGTGACCGACCCAGAGAATG  
TCAAGAGGACTGCCCAGTGGGTGAAGAACCAAGTTGGGGAGAAAGGTCTCTGGGGTCTGATCA  
ATAATGCTGGTGTTCCCGGCGTGCTGGCTCCCACTGACTGGCTGACACTAGAGGACTACAGAG  
AACCTATTGAAGTGAACCTGTTTGGACTCATCAGTGTGACACTAAATATGCTTCCTTTGGTCA  
AGAAAGCTCAAGGGAGAGTTATTAATGTCTCCAGTGTTGGAGGTCGCCTTGCAATCGTTGGAG  
GGGGCTATACTCCATCCAAATATGCAGTGGAAGGTTTCAATGACAGCTTAAGACGGGACATGA  
AAGCTTTTGGTGTGCACGTCTCATGCATTGAACCAGGATTGTTCAAAACAAACTTGGCAGATC  
CAGTAAAGGTAATTGAAAAAAACTCGCCATTTGGGAGCAGCTGTCTCCAGACATCAAACAAC  
AATATGGAGAAGGTTACATTGAAAAAGTCTAGACAAACTGAAAGGCAATAAATCCTATGTGA  
ACATGGACCTCTCTCCGGTGGTAGAGTGCATGGACCACGCTCTAACAAGTCTCTTCCCTAAGA  
CTCATTATGCCGCTGGAAAAGATGCCAAAATTTTCTGGATACCTCTGTCTCACATGCCAGCAG  
CTTTGCAAGACTTTTTATTGTTGAAACAGAAAGCAGAGCTGGCTAATCCCAAGGCAGTGTGAC  
TCAGCTAACCACAAATGTCTCCTCCAGGCTATGAAATTGGCCGATTTCAAGAACACATCTCCT  
TTTCAACCCCATTCCTTATCTGCTCCAACCTGGACTCATTTAGATCGTGCTTATTTGGATTGC  
AAAAGGGAGTCCCACCATCGCTGGTGGTATCCCAGGGTCCCTGCTCAAGTTTTCTTTGAAAAG  
GAGGGCTGGAATGGTACATCACATAGGCAAGTCCTGCCCTGTATTTAGGCTTTGCCTGCTTGG  
TGTGATGTAAGGGAAATTGAAAGACTTGCCCATTCAAAATGATCTTTACCGTGGCCTGCCCCA  
TGCTTATGGTCCCCAGCATTTACAGTAACTTGTGAATGTTAAGTATCATCTCTTATCTAAATA  
TTAAAAGATAAGTCAACCCAAA

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**FIGURE 20**

MLFWVLGLLILCGFLWTRKGLKIEDITDKYIFITGCDSGFGNLAARTFDKKGFHVIAACLTE  
SGSTALKAETSERLRTVLLDVTDPENVKRTAQWVKVQVGEKGLWGLINNAGVPGVLAPTDWLT  
LEDYREPIEVNLFGLISVTNLNMLPLVKKAQGRVINVSSVGGRLAIVGGGYTPSKYAVEGFNDS  
LRRDMKAFGVHVSCEPGLFKTNLADPVKVIEKKLAIWEQLSPDIKQQYGEgyIEKSLDKLKG  
NKSyVNMdLSPVVECDHALTSLFpkThYAAGKDAKIFWIPLSHMPAALQDFLLLKQKAELAN  
PKAV

**Important features of the protein:****Signal peptide:**

amino acids 1-17

**Transmembrane domain:**

amino acids 136-152

**N-glycosylation sites.**

amino acids 161-163, 187-190 and 253-256

**Glycosaminoglycan attachment site.**

amino acids 39-42

**N-myristoylation sites.**

amino acids 36-41, 42-47, 108-113, 166-171, 198-203 and 207-212

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**FIGURE 21**

CTGAGGCGGCGGTAGC**ATG**GAGGGGGAGAGTACGTCGGCGGTGCTCTCGGGCTTTGTGCTCGG  
CGCACTCGCTTTCCAGCACCTCAACACGGACTCGGACACGGAAGGTTTTCTTCTTGGGGAAGT  
AAAAGGTGAAGCCAAGAACAGCATTACTGATTCCCAAATGGATGATGTTGAAGTTGTTTATAC  
AATTGACATT CAGAAATATATTCCATGCTATCAGCTTTT TAGCTTTTATAATTCTTCAGGCGA  
AGTAAATGAGCAAGCACTGAAGAAAATATTATCAAATGTCAAAAAGAATGTGGTAGGTTGGTA  
CAAATTCGGTCGTCATT CAGATCAGATCATGACGTTTAGAGAGAGGCTGCTTCACAAAACTT  
GCAGGAGCATTTTTCAAACCAAGACCTTGTTTTTCTGCTATTAAACACCAAGTATAATAACAGA  
AAGCTGCTCTACTCATCGACTGGAACATTCCTTATATAAACCTCAAAAAGGACTTTTTTCACAG  
GGTACCTTTAGTGTTGCCAATCTGGGCATGTCTGAACAACTGGGTATATAAACTGTATCAGG  
TTCTGTATGTCCACTGGTTTTAGCCGAGCAGTACAAACACACAGCTCTAAATTTTTTGAAGA  
AGATGGATCCTTAAAGGAGGTACATAAGATAAATGAAATGTATGCTTCATTACAAGAGGAATT  
AAAGAGTATATGCAAAAAAGTGGAAGACAGTGAACAAGCAGTAGATAAACTAGTAAAGGATGT  
AAACAGATTAAAACGAGAAATTGAGAAAAGGAGAGGAGCACAGATTCAGGCAGCAAGAGAGAA  
GAACATCCAAAAAGACCCTCAGGAGAACATTTTTCTTGT CAGGCATTACGGACCTTTTTTCC  
AAATTCTGAATTTCTTCATTCATGTGTTATGTCTTTAAAAAATAGACATGTTTCTAAAAGTAG  
CTGTA ACTACAACCACCATCTCGATGTAGTAGACAATCTGACCTTAATGGTAGAACACACTGA  
CATTCCTGAAGCTAGTCCAGCTAGTACACCACAAATCATTAAGCATAAAGCCTTAGACTTAGA  
TGACAGATGGCAATTC AAGAGATCTCGGTTGTTAGATACACAAGACAAACGATCTAAAGCAAA  
TACTGGTAGTAGTAACCAAGATAAAGCATCCAAATGAGCAGCCCAGAAACAGATGAAGAAAT  
TGAAAAGATGAAGGGTTTTGGTGAATATTCACGGTCTCCTACATTT**TGAT**CCTTTTAACCTTA  
CAAGGAGATTTTTTTATTTGGCTGATGGGTAAAGCCAAACATTTCTATTGTTTTTACTATGTT  
GAGCTACTTGCAGTAAGTTCATTTGTTTTTACTATGTTACCTGTTTGCAGTAATACACAGAT  
AACTCTTAGTGCATTTACTTCACAAAGTACTTTTTCAAACATCAGATGCTTTTATTTCCAAAC  
CTTTTTTTCACCTTTC ACTAAGTTGTTGAGGGGAAGGCTTACACAGACACATTCTTTAGAATT  
GGAAAAGTGAGACCAGGCACAGTGGCTCACACCTGTAATCCCAGCACTTAGGGAAGACAAGTC  
AGGAGGATTGATTGAAGCTAGGAGTTAGAGACCAGCCTGGGCAACGTATTGAGACCATGTCTA  
TTAAAAAATAAAATGGAAAAGCAAGAATAGCCTTATTTTCAAATATGGAAAGAAATTTATAT  
GAAAATTTATCTGAGTCATTAAAATTCTCCTTAAGTGATACTTTTTTAGAAGTACATTATGGC  
TAGAGTTGCCAGATAAAATGCTGGATATCATGCAATAAATTTGCAAAACATCATCTAAAATTT  
AAAAAAAAAAAAAAAAAAAAA

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**FIGURE 22**

MEGESTSAVLSGFVLGALAFQHLNTDSDTEGFLGGEVKGEAKNSITDSQMDDVEVVYTIDIQK  
YIPCYQLFSFYNSSGEVNEQALKKILSNVKKNVVGWYKFERRHSDQIMTFRERLLHKNLQEHFS  
NQDLVFLLLTPSIITESCSTHRLEHSLYKPQKGLFHRVPLVVANLGMSEQLGYKTVSGSCMST  
GFSRAVQTHSSKFFEEEDGSLKEVHKINEMYASLQEELKSICKKVEDSEQAVDKLVKDVNRLKR  
EIEKRGAQIQAAAREKNIQKDPQENIFLCQALRTFFPNSEFLHSCVMSLKNRHVSKSSCNYNH  
HLDVVDNLTLMVEHTDIPEASPASTPQIIKHKALDLDLRWQFKRSRLLDLTQDKRSKANTGSSN  
QDKASKMSSPETDEEIEKMKGFGEYSRSPTE

**Important features:****Signal peptide:**

amino acids 1-19

**N-glycosylation sites.**

amino acids 75-79, 322-326

**N-myristoylation site.**

amino acids 184-154

**Growth factor and cytokines receptors family.**

amino acids 134-150



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**FIGURE 23**

GGCACAGCCGCGCGGCGGAGGGCAGAGTCAGCCGAGCCGAGTCCAGCCGGACGAGCGGACCAGCGCAGGGCAGCC  
CAAGCAGCGCGCAGCGAACGCCCCGCGCCGCCACACCCCTCTGCGGTCCCCGCGGCGCCTGCCACCCCTCCCTCC  
TTCCCCGCGTCCCCGCTCGCCGGCCAGTCAGCTTGCCGGGTTCGCTGCCCCGCGAAACCCCGAGGTCACCAGCC  
CGCGCCTCTGCTTCCCTGGGCGCGCGCCGCTCCACGCCCTCCTTCTCCCCTGGCCCGGCGCCTGGCACCAGGGG  
ACCGTTGCCTGACGCGAGGGCCAGCTCTACTTTTCGCCCCGCGTCTCCTCCGCCCTGCTCGCCTCTTCCACCAACT  
CCAACCTCCTTCTCCCTCCAGCTCCACTCGCTAGTCCCCGACTCCGCCAGCCCTCGGCCCGCTGCCGTAGCGCCG  
TTCCCGTCCGGTCCCAAAGGTGGGAACGCGTCCGCCCGGCCCGCACC**ATG**GACGGTTGGGCTTGCCCGCGCTT  
CTCTGCACCCTGGCAGTGCTCAGCGCCGCGCTGCTGGCTGCCGAGCTCAAGTCGAAAAGTTGCTCGGAAGTGCGA  
CGTCTTTACGTGTCCAAAGGCTTCAACAAGAACGATGCCCCCTCCACGAGATCAACGGTGATCATTGAAGATC  
TGTCGCCAGGGTTCTACCTGCTGCTCTCAAGAGATGGAGGAGAAGTACAGCCTGCAAAGTAAAGATGATTTCAA  
AGTGTGGTCAGCGAACAGTGCAATCATTGCAAGCTGTCTTTGCTTACGTTACAAGAAGTTTGATGAATCTTC  
AAAGAACTACTTGAAAATGCAGAGAAATCCCTGAATGATATGTTTGTGAAGACATATGGCCATTTATACATGCAA  
AATTCTGAGCTATTTAAAGATCTCTTCGTAGAGTTGAAACGTTACTACGTGGTGGGAAATGTGAACCTGGAAGAA  
ATGCTAAATGACTTCTGGGCTCGCTCCTGGAGCGGATGTTCCGCCCTGGTGAACCTCCAGTACCCTTTACAGAT  
GAGTATCTGGAATGTGTGAGCAAGTATACGGAGCAGCTGAAGCCCTTCGGAGATGTCCCTCGCAAATTGAAGCTC  
CAGGTTACTCGTGCTTTTGTAGCAGCCGCTACTTTTCGCTCAAGGCTTAGCGGTTGCCGGGAGATGTCGTGAGCAAG  
GTCTCCGTGGTAAACCCACAGCCAGTGTAACCATGCCCTGTTGAAGATGATCTACTGCTCCCACTGCCGGGGT  
CTCGTGACTGTGAAGCCATGTTACAATACTGCTCAAACATCATGAGAGGCTGTTTGGCCAACCAAGGGGATCTC  
GATTTTGAATGGAACAATTTCATAGATGCTATGCTGATGGTGGCAGAGAGGCTAGAGGGTCCTTTCAACATTGAA  
TCGGTCATGGATCCCATCGATGTGAAGATTTCTGATGCTATTATGAACATGCAGGATAATAGTGTTCAGTGTCT  
CAGAAGGTTTTCCAGGGATGTGGACCCCCCAAGCCCTCCAGCTGGACGAATTTCTCGTTCCATCTCTGAAAGT  
GCCTTCAGTGCTCGCTTCAGACCACATCACCCGAGGAACGCCCAACCACAGCAGCTGGCACTAGTTTGGACCGA  
CTGGTTACTGATGTCAAGGAGAACTGAAACAGGCCAAGAAATTCTGGTCCCTCCCTTCGAGCAACGTTTGCAAC  
GATGAGAGGATGGCTGCAGGAAACGGCAATGAGGATGACTGTTGGAATGGGAAAGGCAAAAGCAGGTACCTGTTT  
GCAGTGACAGGAAATGGATTAGCCAACAGGGCAACAACCCAGAGGTCCAGGTTGACACCAGCAAACAGACATA  
CTGATCCTTCGTCAAATCATGGCTCTTCGAGTGATGACCAGCAAGATGAAGAATGCATACAATGGGAACGACGTG  
GACTTCTTTGATATCAGTGATGAAAGTAGTGGAGAAGGAAGTGGAAAGTGGCTGTGAGTATCAGCAGTGCCCTTCA  
GAGTTTGACTACAATGCCACTGACCATGCTGGGAAGAGTGCCAATGAGAAAGCCGACAGTGCTGGTGTCCGTCTT  
GGGGCACAGGCCTACCTCCTCACTGTCTTCTGCATCTTGTTCTTGTTATGCAGAGAGAGTGGAGAT**TA**ATTCTCA  
AACTCTGAGAAAAAGTGTTTCATCAAAAAGTTAAAAGGCACCAGTTATCACTTTTCTACCATCCTAGTGACTTTGC  
TTTTTAAATGAATGGACAACAATGTACAGTTTTTACTATGTGGCCACTGGTTTAAGAAGTGTGACTTTGTTTTT  
TCATTCAGTTTTTGGGAGGAAAAGGGACTGTGCATTGAGTTGGTTTCCTGCTCCCCCAAACCATGTTAAACGTGGCT  
AACAGTGTAGGTACAGAACTATAGTTAGTTGTGCATTTGTGATTTTATCACTCTATTATTTGTTGTATGTTTTT  
TTCTCATTTTCGTTTGTGGGTTTTTTTTTCCAACGTGATCTCGCCTTGTTTCTTACAAGCAAACAGGGTCCCTT  
CTTGGCACGTAACATGTACGTATTTCTGAAATATTAAATAGCTGTACAGAAGCAGGTTTTATTTATCATGTTATC  
TTATTAAAAGAAAAAGCCCAAAAGC

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**FIGURE 24**

MARFGLPALLCTLAVLSAALLAELKSKSCSEVRRLYVSKGFNKNDAPLHEINGDHLKICPQG  
STCCSQEMEKEYSLQSKDDFKSVVSEQCNHLQAVFASRYKKFDEFFKELLENAEKSLNDMFVK  
TYGHLYMQNSSELFKDLFVELKRYIVVGNVNLEEMLNDFWARLLERMFLVNSQYHFTDEYLEC  
VSKYTEQLKPFQDVPRKLKLQVTRAFVAARTFAQGLAVAGDVVSKVSVVNPTAQCTHALLKMI  
YCSHCRGLVTVKPCYNYCSNIMRGCLANQGDLD FEWNNFIDAMLMVAERLEGPFNIESVMDPI  
DVKISDAIMNMQDNSVQVSQKVFQCGPPKPLPAGRISRSISESAFSARFRPHHPEERPTTAA  
GTSLDRLVTDVKEKLKQAKKFWSSSLPSNVCNDERMAAGNGNEDDCWNGKGKSRYLFAVTGNGL  
ANQGNNEPVQVDTSKPDILILRQIMALRVMTSKMKNAYNGNDVDFDISDESSGEGSGSGCEY  
QQCPSEFDYNATDHAGKSANEKADSAGVRPGAQAYLLTVFCILFLVMQREWR

**Important features:****Signal peptide:**

amino acids 1-22

**ATP/GTP-binding site motif A (P-loop).**

amino acids 515-524

**N-glycosylation site.**

amino acids 514-518

**Glycosaminoglycan attachment sites.**

amino acids 494-498, 498-502

**N-myristoylation sites.**

amino acids 63-69, 224-230, 276-282, 438-444, 497-503, 531-537

**Glypicans proteins.**

amino acids 54-75, 105-157, 238-280, 309-346, 423-460, 468-506

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**FIGURE 25**

CTCGCCCTCAAATGGGAACGCTGGCCTGGGACTAAAGCATAGACCACCAGGCTGAGTATCCTG  
ACCTGAGTCATCCCCAGGGATCAGGAGCCTCCAGCAGGGAACCTTCCATTATATTCTTCAAGC  
AACTTACAGCTGCACCGACAGTTGCGATGAAAGTTCTAATCTCTTCCCTCCTCCTGTTGCTGC  
CACTAATGCTGATGTCCATGGTCTCTAGCAGCCTGAATCCAGGGGTCGCCAGAGGCCACAGGG  
ACCGAGGCCAGGCTTCTAGGAGATGGCTCCAGGAAGGCGGCCAAGAATGTGAGTGCAAAGATT  
GGTTCCTGAGAGCCCCGAGAAGAAAATTCATGACAGTGTCTGGGCTGCCAAAGAAGCAGTGCC  
CCTGTGATCATTTCAAGGGCAATGTGAAGAAAACAAGACACCAAAGGCACCACAGAAAGCCAA  
ACAAGCATTCAGAGCCTGCCAGCAATTTCTCAAACAATGTCAGCTAAGAAGCTTTGCTCTGC  
CTTTGTAGGAGCTCTGAGCGCCCACTCTTCCAATTAAACATTCTCAGCCAAGAAGACAGTGAG  
CACACCTACCAGACACTCTTCTTCTCCACCTCACTCTCCCACTGTACCCACCCCTAAATCAT  
TCCAGTGCTCTCAAAAAGCATGTTTTTCAAGATCATTTTGTGTTGCTCTCTCTAGTGCTT  
CTTCTCTCGTCAGTCTTAGCCTGTGCCCTCCCCTTACCCAGGCTTAGGCTTAATTACCTGAAA  
GATTCCAGGAACTGTAGCTTCCTAGCTAGTGTCATTTAACCTTAAATGCAATCAGGAAAGTA  
GCAAACAGAAGTCAATAAATATTTTTAAATGTCAAAAAAAAAAAAAAAAAAAAA

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## **FIGURE 26**

MKVLISLLLLLLPLMLMSMVSSSLNPGVARGHRDRGQASRRWLQEGGQECECKDWFLRAPRRK  
FMTVSGLPKKQCPDHFKGNVKKTRHQRHHRKPNKHSRACQQFLKQCQLRSFALPL

**Important features:**

**Signal peptide:**

amino acids 1-22

**N-myristoylation sites.**

amino acids 27-33, 46-52

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**FIGURE 27**

GGACGCCAGCGCCTGCAGAGGCTGAGCAGGGAAAAAGCCAGTGCCCCAGCGGAAGCACAGCTC  
AGAGCTGGTCTGCCATGGACATCCTGGTCCCCTCCTGCAGCTGCTGGTGCTGCTTCTTACCC  
TGCCCCCTGCACCTCATGGCTCTGCTGGGCTGCTGGCAGCCCCTGTGCAAAGCTACTTCCCCT  
ACCTGATGGCCGTGCTGACTCCCAAGAGCAACCGCAAGATGGAGAGCAAGAAACGGGAGCTCT  
TCAGCCAGATAAAGGGGCTTACAGGAGCCTCCGGGAAAGTGGCCCTACTGGAGCTGGGCTGCG  
GAACCGGAGCCAACTTTCAGTTCTACCCACCGGGCTGCAGGGTCACCTGCCTAGACCCAAATC  
CCCCTTTGAGAAGTTCCTGACAAAGAGCATGGCTGAGAACAGGCACCTCCAATATGAGCGGT  
TTGTGGTGGCTCCTGGAGAGGACATGAGACAGCTGGCTGATGGCTCCATGGATGTGGTGGTCT  
GCACTCTGGTGTGTGCTCTGTGCAGAGCCCAAGGAAGGTCCTGCAGGAGGTCCGGAGAGTAC  
TGAGACCGGGAGGTGTGCTCTTTTTCTGGGAGCATGTGGCAGAACCATATGGAAGCTGGGCCT  
TCATGTGGCAGCAAGTTTTTCGAGCCCACCTGGAAACACATTGGGGATGGCTGCTGCCTACCA  
GAGAGACCTGGAAGGATCTTGAGAACGCCCAGTTCTCCGAAATCCAAATGGAACGACAGCCCC  
CTCCCTTGAAGTGGCTACCTGTTGGGCCCCACATCATGGGAAAGGCTGTCAAACAATCTTTCC  
CAAGCTCCAAGGCACTCATTTGCTCCTTCCCCAGCCTCCAATTAGAACAAGCCACCCACCAGC  
CTATCTATCTTCCACTGAGAGGGACCTTAGCAGAATGAGAGAAGACATTCATGTACCACCTACT  
AGTCCCTCTCTCCCCAACCTCTGCCAGGGCAATCTCTAACTTCAATCCCGCCTTCGACAGTGA  
AAAAGCTCTACTTCTACGCTGACCCAGGGAGGAAACACTAGGACCCTGTTGTATCCTCAACTG  
CAAGTTTCTGGACTAGTCTCCCAACGTTTGCCTCCCAATGTTGTCCCTTTCCTTCGTTCCCAT  
GGTAAAGCTCCTCTCGCTTTCCTCCTGAGGCTACACCCATGCGTCTCTAGGAACTGGTCACAA  
AAGTCATGGTGCCTGCATCCCTGCCAAGCCCCCTGACCCTCTCTCCCCACTACCACCTTCTT  
CCTGAGCTGGGGGCACCAGGGAGAATCAGAGATGCTGGGGATGCCAGAGCAAGACTCAAAGAG  
GCAGAGGTTTTGTTCTCAAATATTTTTTAATAAATAGACGAAACCACG

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**FIGURE 28**

MDIILVPELLQLLVLLLTPLHLMALLGCWQPLCKSYFPYLMAVLTPKSNRKMESKKRELFSSQIK  
GLTGASGKVALLELGCCTGANFQFYPPGCRVTCCLDPNPHFEKFLTKSMAENRHLQYERFVVAP  
GEDMRQLADGSMDDVVCTLVLCSSVQSPRKVLQEVRRVLRPGGVLFWEHVAEPYGSWAFMWQQ  
VFEPTWKHIGDGCCLTRETWKDLENAQFSEIQMERQPPPLKWLPGPHIMGKAVKQSFSSKA  
LICSFPSLQLEQATHQPIYLPLRGT

**Important features:****Signal peptide:**

amino acids 1-23

**Leucine zipper pattern.**

amino acids 10-32

**N-myristoylation sites.**

amino acids 64-70, 78-84, 80-86, 91-97, 201-207

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**FIGURE 29**

CAATGTTTGCCTATCCACCTCCCCCAAGCCCCTTTACCTATGCTGCTGCTAACGCTGCTGCTG  
CTGCTGCTGCTGCTTAAAGGCTCATGCTTGGAGTGGGGACTGGTCGGTGCCCAGAAAGTCTCT  
TCTGCCACTGACGCCCCCATCAGGGATTGGGCCTTCTTTCCCCCTTCCTTTCTGTGTCTCCTG  
CCTCATCGGCCTGCCATGACCTGCAGCCAAGCCCAGCCCCGTGGGGAAGGGGAGAAAGTGGGG  
GATGGCTAAGAAAGCTGGGAGATAGGGAACAGAAGAGGGTAGTGGGTGGGCTAGGGGGGCTGC  
CTTATTTAAAGTGGTTGTTTATGATTCTTATACTAATTTATACAAAGATATTAAGGCCCTGTT  
CATTAAAGAAATTGTTCCCTTCCCCTGTGTTCAATGTTTGTAAAGATTGTTCTGTGTAAATATG  
TCTTTATAATAAACAGTTAAAAGCTGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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## **FIGURE 30**

MLLLTLLLLLLLLLKGSCLEWGLVGAQKVSSATDAPIRDWAFPPSFLCLLPHRPAMTCSQAQP  
RGEGEKVG DG

**Important features:**

**Signal peptide:**

amino acids 1-15

**Growth factor and cytokines receptors family:**

amino acids 3-18



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**FIGURE 31**

GTTTGAATTCCTTCAACTATACCCACAGTCCAAAAGCAGACTCACTGTGTCCCAGGCTACCAG  
TTCCTCCAAGCAAGTCATTTCCCTTATTTAACCGATGTGTCCCTCAAACACCTGAGTGCTACT  
CCCTATTTGCATCTGTTTTGATAAATGATGTTGACACCCTCCACCGAATTCTAAGTGGAAATCA  
TGTCGGGAAGAGATAACAATCCTTGGCCTGTGTATCCTCGCATTAGCCTTGTCTTTGGCCATGA  
TGTTTACCTTCAGATTCATCACCACCCTTCTGGTTCACATTTTCATTTCAATTGGTTATTTTGG  
GATTGTTGTTTGTCTGCGGTGTTTTATGGTGGCTGTATTATGACTATAACCAACGACCTCAGCA  
TAGAATTGGACACAGAAAGGGAAATATGAAGTGCCTGCTGGGGTTTGCTATCGTATCCACAG  
GCATCACGGCAGTGCTGCTCGTCTTGATTTTTGTTCTCAGAAAGAGAATAAAATTGACAGTTG  
AGCTTTTCCAAATCACAAATAAAGCCATCAGCAGTGCTCCCTTCCTGCTGTTCCAGCCACTGT  
GGACATTTGCCATCCTCATTTTCTTCTGGGTCCTCTGGGTGGCTGTGCTGCTGAGCCTGGGAA  
CTGCAGGAGCTGCCCAGGTTATGGAAGGCGGCCAAGTGGAATATAAGCCCCTTTCGGGCATTTC  
GGTACATGTGGTCGTACCATTTAATTGGCCTCATCTGGACTAGTGAATTCATCCTTGCGTGCC  
AGCAAATGACTATAGCTGGGGCAGTGGTTACTTGTTATTTCAACAGAAGTAAAAATGATCCTC  
CTGATCATCCCATCCTTTCGTCTCTCTCCATTCTCTTCTTCTACCATCAAGGAACCGTTGTGA  
AAGGGTCATTTTTTAATCTCTGTGGTGAGGATTCGGAGAATCATTGTCATGTACATGCAAAACG  
CACTGAAAGAACAGCAGCATGGTGCAATTGTCCAGGTACCTGTTCCGATGCTGCTACTGCTGTT  
TCTGGTGTCTTGACAAATACCTGCTCCATCTCAACCAGAATGCATATACTACAACCTGCTATTA  
ATGGGACAGATTTCTGTACATCAGCAAAAGATGCATTCAAATCCTTGTTCCAAGAACTCAAGTC  
ACTTTACATCTATTAACCTGCTTTGGAGACTTCATAATTTTTCTAGGAAAGGTGTTAGTGGTGT  
GTTTCACTGTTTTTGGAGGACTCATGGCTTTTAACTACAATCGGGCATTCCAGGTGTGGGCAG  
TCCCTCTGTTATTGGTAGCTTTTTTTGCCTACTTAGTAGCCCATAGTTTTTTATCTGTGTTTG  
AAACTGTGCTGGATGCACTTTTCCTGTGTTTTGCTGTTGATCTGGAAACAAATGATGGATCGT  
CAGAAAAGCCCTACTTTATGGATCAAGAATTTCTGAGTTTCGTAAAAGGAGCAACAAATTAA  
ACAATGCAAGGGCACAGCAGGACAAGCACTCATTAAGGAATGAGGAGGGAACAGAACTCCAGG  
CCATTGTGAGATAGATACCCATTTAGGTATCTGTACCTGGAAAACATTTCTTCTAAGAGCCA  
TTTACAGAATAGAAGATGAGACCACTAGAGAAAAGTTAGTGAATTTTTTTTTTAAAGACCTAA  
TAAACCCTATTCTTCCTCAAAA

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**FIGURE 32**

MSGRDTILGLCILALALSLAMMFTFRFITLLVHIFISLVILGLLFVCGVLWWLYDYTDNLS  
IELDTERENMKCVLGFAIVSTGITAVLLVLI FVLRKRIKLTVELFQITNKAISSAPFLLFQPL  
WTFAILIFFWVLWVAVLLSLGTAGAAQVMEGGQVEYKPLSGIRYMWSYHLIGLIWTSEFILAC  
QQMTIAGAVVTCYFNRSKNDPPDHPILSSLSILFFYHQGTVVKGSFLISVVRIPRIIVMYMQN  
ALKEQQHGALSRYLFRCCYCCFWCLDKYLLHLNQAYTTTAINGTDFCTSAKDAFKILSKNSS  
HFTSINCFGDFIIFLGKVLVVCFTVFGGLMAFNYNRAFQVWAVPLLLVAFFAYLVAHSFLSVF  
ETVLDALFLCFAVDLETNDGSSEKPYFMDQEFLSFVKRSNKLNNARAQQDKHSLRNEEGTELQ  
AIVR

**Important features:****Signal peptide:**

amino acids 1-20

**Putative transmembrane domains:**

amino acids 35-54, 75-97, 126-146, 185-204, 333-350, 352-371

**N-glycosylation sites.**

amino acids 204-208, 295-299, 313-317

**N-myristoylation sites.**

amino acids 147-153, 178-184, 196-202, 296-275, 342-348

[illegible]

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**FIGURE 34**

MRTVVLTMKASVIEMFLVLLVTGVHSNKETAKKIKRPKFTVPQINCDVKAGKIIDPEFIVKCP  
AGCQDPKYHVGTDVYASYSSVCGAAVHSGVLDNSGGKILVRKVAGQSGYKGSYSNGVQSLSL  
PRWRESFIVLESKPKKGVITYPSALTYSSSKSPAAQAGETTKAYQRPPIPGTTAQPVTLMQLLA  
VTVAVATPTTLPRPSPSAASTTSIPRPQSVGHRSEQEMDLWSTATYTSSQNRPRADPGIQRQDP  
SGAAFQKPVGADVSLGLVPKEELSTQSLEPVSLGDPNCKIDLSFLIDGSTSIGKRRFRIQKQL  
LADVAQALDIGPAGPLMGVVQYGDNPATHFNLKTHTNSRDLKTAIEKITQRGGLSNVGRAISF  
VTKNFFSKANGNRSGAPNVVVVMVDGWPTDKVEEASRLARESGINIFFITIEGAAENEKQYVV  
EPNFANKAVCRTNGFYSLHVQSWFGLHKTLLQPLVKRVCDTDLACSKTCLNSADIGFVIDGSS  
SVGTGNFRTVLQFVTNLTKEFEISDTRIGAVQYTYEQRLDFGFDKYSSKPDILNAIKRVGY  
WSGGTSTGAAINFALEQLFKKSKPNKRKLMILITDGRSYDDVRI PAMAAHLKGVITYAIGVAW  
AAQEELEVIATHPARDHSFFVDEFDNLHQYVPRIIQNICTEFNSQPRN

**Important features:****Signal peptide:**

amino acids 1-26

**Transmembrane domain:**

amino acids 181-200

**N-glycosylation sites.**

amino acids 390-394, 520-524

**N-myristoylation sites.**amino acids 23-29, 93-99, 115-121, 262-268, 367-373, 389-395,  
431-437, 466-472, 509-515, 570-576, 571-577, 575-581, 627-633**Amidation site.**

amino acids 304-308

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**FIGURE 35**

CCGAGCACAGGAGATTGCCTGCGTTTAGGAGGTGGCTGCGTTGTGGGAAAAGCTATCAAGGAA  
GAAATTGCCAAACCATGTCTTTTTTCTGTTTTTCAGAGTAGTTCACAACAGATCTGAGTGTTT  
TAATTAAGCATGGAATACAGAAAACAACAAAAAAGCTTAAGCTTTAATTTTCATCTGGAATTCCA  
CAGTTTTCTTAGCTCCCTGGACCCGGTTGACCTGTTGGCTCTTCCCGCTGGCTGCTCTATCAC  
GTGGTGCTCTCCGACTACTCACCCCGAGTGTAAGAACCTTCGGCTCGCGTGCTTCTGAGCTG  
CTGTGGATGGCCTCGGCTCTCTGGACTGTCCTTCCGAGTAGGATGTCACTGAGATCCCTCAAA  
TGGAGCCTCCTGCTGCTGTCACTCCTGAGTTTCTTTGTGATGTGGTACCTCAGCCTTCCCCAC  
TACAATGTGATAGAACGCGTGAAGTGGATGTACTTCTATGAGTATGAGCCGATTTACAGACAA  
GACTTTCACCTTCACACTTCGAGAGCATTCAAAGTCTCTCATCAAAATCCATTTCTGGTCATT  
CTGGTGACCTCCCACCCTTCAGATGTGAAAGCCAGGCAGGCCATTAGAGTTACTTGGGGTGAA  
AAAAAGTCTTGGTGGGGATATGAGGTTCTTACATTTTCTTATTAGGCCAAGAGGCTGAAAAG  
GAAGACAAAATGTTGGCATTGTCCTTAGAGGATGAACACCTTCTTTATGGTGACATAATCCGA  
CAAGATTTTTTAGACACATATAATAACCTGACCTTGAAAACCATTATGGCATTACAGGTGGGTG  
ACTGAGTTTTGCCCCAATGCCAAGTACGTAATGAAGACAGACACTGATGTTTTTCATCAATACT  
GGCAATTTAGTGAAGTATCTTTTAAACCTAAACCACTCAGAGAAGTTTTTCACAGGTATCCT  
CTAATTGATAATTATTCCTATAGAGGATTTTACCAAAAAACCCATATTTCTTACCAGGAGTAT  
CCTTTCAAGGTGTTCCCTCCATACTGCAGTGGGTTGGGTTATATAATGTCCAGAGATTTGGTG  
CCAAGGATCTATGAAATGATGGGTCACGTAAAACCCATCAAGTTTGAAGATGTTTATGTCGGG  
ATCTGTTTGAATTTATTAAAAGTGAACATTCATATTCCAGAAGACACAAATCTTTTCTTTCTA  
TATAGAATCCATTTGGATGTCTGTCAACTGAGACGTGTGATTGCAGCCCATGGCTTTTCTTCC  
AAGGAGATCATCACTTTTTTGGCAGGTCATGCTAAGGAACACCACATGCCATTATTAACTTCAC  
ATTCTACAAAAAGCCTAGAAGGACAGGATACCTTGTGGAAAGTGTTAAATAAAGTAGGTACTG  
TGGAAAATTCATGGGGAGGTCAGTGTGCTGGCTTACACTGAACTGAAACTCATGAAAAACCA  
GACTGGAGACTGGAGGGTTACACTTGTGATTTATTAGTCAGGCCCTTCAAAGATGATATGTGG  
AGGAATTAAATATAAAGGAATTGGAGGTTTTTGCTAAAGAAATTAATAGGACCAAACAATTTG  
GACATGTCATTCTGTAGACTAGAATTTCTTAAAAGGGTGTTACTGAGTTATAAGCTCACTAGG  
CTGTAAAAACAAAACAATGTAGAGTTTTATTTATTGAACAATGTAGTCACTTGAAGGTTTTGT  
GTATATCTTATGTGGATTACCAATTTAAAAATATATGTAGTTCTGTGTCAAAAACTTCTTCA  
CTGAAGTTATACTGAACAAAATTTTACCTGTTTTTGGTCATTTATAAAGTACTTCAAGATGTT  
GCAGTATTTACAGTTATTATTATTAAAATTACTTCAACTTTGTGTTTTTAAATGTTTTGAC  
GATTTCAATACAAGATAAAAAGGATAGTGAATCATTCTTTACATGCAACATTTTCCAGTTAC  
TTAACTGATCAGTTTATTATTGATACATCACTCCATTAATGTAAAGTCATAGGTCATTATTGC  
ATATCAGTAATCTCTTGGACTTTGTAAATATTTTACTGTGGTAATATAGAGAAGAATTAAAG  
CAAGAAAATCTGAAAA

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**FIGURE 36**

MASALWTVLPSRMSLRSLKWSLLLLSLLSFFVMWYLSLPHYNVIERVNWMYFYEYEPYRQDF  
HFTLREHSNCSHQNPFLVILVTSHPSDVKARQAIRVTWGEKKSWWGYEVLTFLLGQEAEKED  
KMLALSLEDEHLLYGDIIRQDFLDITYNNLTTLKTIMAFRWVTEFCPNAKYVMKTDTDVFINTGN  
LVKYLLNLNHSEKFFTGYPLIDNYSYRGFYQKTHISYQEYPFKVFPPYCSGLGYIMSRDLVPR  
IYEMMGHVKPIKFEDVYVGICLNLLKVNIIHIPEDTNLFFLYRIHLDVCQLRRVIAAHGFSSKE  
IITFWQVMLRNTTCHY

**Important features:****Type II transmembrane domain:**

amino acids 20-39

**N-glycosylation sites.**

amino acids 72-76, 154-158, 198-202, 212-216, 326-330

**Glycosaminoglycan attachment site.**

amino acids 239-243

**Ly-6 / u-PAR domain proteins.**

amino acids 23-37

**N-myristoylation site.**

amino acids 271-277

### FIGURE 37

[illegible]

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**FIGURE 38**

MELGCWTQLGLTFLQLLLISSLPREYTVINEACPGAENIMCRECCEYDQIECVCPGKREVVG  
YTIPCCRNEENECDSCLIHPGCTIFENCKSCRNGSWGGLDDFYVKGFYCAECRAGWYGGDCM  
RCGQVLRAPKGQILLESYPLNAHCEWTIHAKPGFVIQLRFVMLSLEFDYMCQYDYVEVRDGDN  
RDGQIIKRVCGNERPAPIQSIGSSLHVLFHSDGSKNFDGFHAIYEEITACSSSPCFHDGTCVL  
DKAGSYKACLAGYTGQRCENLLEERNCSDPGGPVNGYQKITGGPGLINGRHAKIGTVVSFFC  
NNSYVLSGNEKRTCQQNGEWSGKQPICIKACREPKISDLVRRRVLPQVQSRETPLHQLYSAA  
FSKQKLQSAPTKKPALPFGDLPMGYQHLHTQLQYECISPFYRRLGSSRRTCLRTGKWSGRAPS  
CIPICGKIENITAPKTQGLRWPWQAIIYRRTSGVHDGSLHKGAWFLVCSGALVNERTVVVAAH  
CVTDLGKVTMIKTADLKVVLGKFYRDDDRDEKTIQSLQISAIILHPNYDPILLDADIAILKLL  
DKARISTRVQPICLAASRDLSFSQESHITVAGWNVLADVRSPGFKNLTLRSGVVSVDLLC  
EEQHEDHGIPVSVTDNMFCASWEPTAPSDICTAETGGIAAVSFPGRASPEPRWHLMGLVSWSY  
DKTCSHRLSTAFTKVLFPKDWIERNMK

**Important features of the protein:****Signal peptide:**

amino acids 1-23

**EGF-like domain cysteine pattern signature.**

amino acids 260-272

**N-glycosylation sites.**

amino acids 96-100, 279-283, 316-320, 451-455, 614-618

**N-myristoylation sites.**amino acids 35-41, 97-103, 256-262, 284-290, 298-304, 308-314,  
474-480, 491-497, 638-644, 666-672**Amidation site.**

amino acids 56-60

**Serine proteases, trypsin family.**

amino acids 489-506

**CUB domain proteins profile.**

amino acids 150-167



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**FIGURE 39**

GGTTCCTACATCCTCTCATCTGAGAATCAGAGAGCATAATCTTCTTACGGGCCCGTGATTTATTAACGTGGCTTA  
ATCTGAAGGTTCTCAGTCAAATTCTTTGTGATCTACTGATTGTGGGGGCATGGCAAGGTTTGCTTAAAGGAGCTT  
GGCTGGTTTGGGCCCTTGTAGCTGACAGAAGGTGGCCAGGGAGAATGCAGCACACTGCTCGGAGAATGAAGGCGC  
TTCTGTTGCTGGTCTTGCCCTGGCTCAGTCCTGCTAACTACATTGACAATGTGGGCAACCTGCACTTCCTGTATT  
CAGAACTCTGTAAAGGTGCCTCCCACTACGGCCTGACCAAAGATAGGAAGAGGCGCTCACAAGATGGCTGTCCAG  
ACGGCTGTGCGAGCCTCACAGCCACGGCTCCCTCCCCAGAGGTTTCTGCAGCTGCCACCATCTCCTTAATGACAG  
ACGAGCCTGGCCTAGACAACCCTGCCTACGTGTCTCGGCAGAGGACGGGCAGCCAGCAATCAGCCCAGTGGACT  
CTGGCCGGAGCAACCGAACTAGGGCACGGCCCTTTGAGAGATCCACTATTAGAAGCAGATCATTTAAAAAATAA  
ATCGAGCTTTGAGTGTCTTTCGAAGGACAAAGAGCGGGAGTGCAGTTGCCAACCATGCCGACCAGGGCAGGGAAA  
ATTCTGAAAACACCACTGCCCCCTGAAGTCTTTCCAAGGTTGTACCACCTGATTCCAGATGGTGAAATTACCAGCA  
TCAAGATCAATCGAGTAGATCCCAGTGAAGCCTCTCTATTAGGCTGGTGGGAGGTAGCGAAACCCCACTGGTCC  
ATATCATTATCCAACATTTATCGTGATGGGGTGATCGCCAGAGACGGCCGGCTACTGCCAGGAGACATCATTC  
TAAAGGTCAACGGGATGGACATCAGCAATGTCCCTCACAACCTACGCTGTGCGTCTCCTGCGGCAGCCCTGCCAGG  
TGCTGTGGCTGACTGTGATGCGTGAACAGAAGTTCGCGCAGCAGGAACAATGGACAGGCCCCGGATGCCTACAGAC  
CCCAGATGACAGCTTTCATGTGATTCTCAACAAAAGTAGCCCCGAGGAGCAGCTTGAATAAACTGGTGCGCA  
AGGTGGATGAGCCTGGGGTTTTTCATCTTCAATGTGCTGGATGGCGGTGTGGCATATCGACATGGTCAGCTTGAGG  
AGAATGACCGTGTGTAGCCATCAATGGACATGATCTTCGATATGGCAGCCAGAAAGTGCGGCTCATCTGATTC  
AGGCCAGTGAAAGACGTGTTACCTCGTCGTGTCCCGCCAGGTTCCGGCAGCGGAGCCCTGACATCTTTCAGGAAG  
CCGGCTGGAACAGCAATGGCAGCTGGTCCCCAGGGCCAGGGGAGAGGAGCAACACTCCCAAGCCCCCTCCATCCTA  
CAATTACTTGTGATGAGAAGGTGGTAAATATCCAAAAAGACCCCGGTGAATCTCTCGGCATGACCGTCGAGGGG  
GAGCATCACATAGAGAATGGGATTTGCCTATCTATGTCATCAGTGTGAGCCCGGAGGAGTCATAAGCAGAGATG  
GAAGAATAAAAAACAGGTGACATTTTGTGAATGTGGATGGGGTCAACTGACAGAGGTGAGCCGGAGTGAGGCAG  
TGGCATTATTGAAAAGAACATCATCCTCGATAGTACTCAAAGCTTTGGAAGTCAAAGAGTATGAGCCCCAGGAAG  
ACTGCAGCAGCCAGCAGCCCTGGACTCCAACCACAACATGGCCCCACCCAGTGACTGGTCCCCATCCTGGGTCA  
TGTGGCTGGAATTACCACGGTGCTTGTATAACTGTAAAGATATTGTATTACGAAGAAACACAGCTGGAAGTCTGG  
GCTTCTGCATTGTAGGAGGTATGAAGAATACAATGGAAACAAACCTTTTTTTCATCAAATCCATTGTTGAAGGAA  
CACCAGCATACAATGATGGAAGAATTAGATGTGGTGATATTCTTCTTGCTGTCAATGGTAGAAGTACATCAGGAA  
TGATACATGCTTGCTTGCAAGACTGCTGAAAGAACTTAAAGGAAGAATTACTCTAACTATTGTTTCTTGGCCTG  
GCATTTTTTTATAGAAATCAATGATGGGTGAGAGGAAAACAGAAAAATCACAATAGGCTAAGAAGTTGAAACACT  
ATATTTATCTGTGAGTTTTTATATTTAAAGAAAGAATACATTGTAAAAATGTCAGGAAAAGTATGATCATCTAA  
TGAAAGCCAGTTACACCTCAGAAAATATGATTCCAAAAAATTAATACTACTAGTTTTTTTTTCAGTGTGGAGGAT  
TTCTCATTACTCTACAACATTGTTTATATTTTTCTATTCAATAAAAAGCCCTAAAACAATAAAATGATTGATT  
TGTATACCCCACTGAATCAAGCTGATTTAAATTTAAATTTGGTATATGCTGAAGTCTGCCAAGGGTACATTAT  
GGCCATTTTTTAATTTACAGCTAAAATATTTTAAAATGCATTGCTGAGAAACGTTGCTTTCATCAAACAAGAAT  
AAATATTTTTTCAGAAGTTAAA

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**FIGURE 40**

MKALLLLVLPWLSPANYIDNVGNLHFLYSELCKGASHYGLTKDRKRRSQDGCPCDGCASLTATA  
PSPEVSAAATISLMTDEPGLDNPAYVSSAEDGQPAISPVDSGRSNRTRARPFERSTIRSRSEK  
KINRALSVLRRTKSGSAVANHADQGRENSSENTTAPEVFPRLYHLIPDGEITSIKINRVDPSES  
LSIRLVGGSETPLVHIIQHIYRDGVIARDGRLLPGDIILKVNGMDISNVPHNYAVRLLRQPC  
QVLWLTVMREQKFRSRNNGQAPDAYRPRDDSFHVILNKSSPEEQLGIKLVKRVDEPGVFIFNV  
LDGGVAYRHGQLEENDRVLAINGHDLRYGSPESAHLIQASERRVHLVVSQRQVRQSPDIFQE  
AGWNSNGSWSPGPGERSNTPKPLHPTITCHEKVVNIQKDPGESLGMTVAGGASHREWDLPYV  
ISVEPGGVISRDGRIKTGDILLNVGVELTEVSRSEAVALLKRTSSSIVLKALEVKEYEPQED  
CSSPAALDSNHNMAPPSDWSPSWVMWLELPRCLYNCKDIVLRRNTAGSLGFCIVGGYEEYNGN  
KPFPIKSIVEGTPAYNDGRIRCGDILLAVNGRSTSGMIHACLARLLKELKGRITLTIVSWPGTFL

**Important features:****Signal peptide:**

amino acids 1-15

**N-glycosylation sites.**

amino acids 108-112, 157-161, 289-293, 384-388

**Tyrosine kinase phosphorylation sites.**

amino acids 433-441, 492-500

**N-myristoylation sites.**amino acids 51-57, 141-147, 233-239, 344-350, 423-429, 447-453,  
467-473, 603-609

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**FIGURE 41**

ACCAGGCATTGTATCTTCAGTTGTCATCAAGTTCGCAATCAGATTGGAAAAGCTCAACTTGAA  
GCTTTCTTGCCTGCAGTGAAGCAGAGAGATAGATATTATTACGTAATAAAAAACATGGGCTT  
CAACCTGACTTTCCACCTTTCCTACAAATTCCGATTACTGTTGCTGTTGACTTTGTGCCTGAC  
AGTGGTTGGGTGGGCCACCAGTAACTACTTCGTGGGTGCCATTCAAGAGATTCCCTAAAGCAAA  
GGAGTTCATGGCTAATTTCCATAAGACCCTCATTTTGGGGAAGGGAAAACTCTGACTAATGA  
AGCATCCACGAAGAAGGTAGAACTTGACAACCTGTCCTTCTGTGTCTCCTTACCTCAGAGGCCA  
GAGCAAGCTCATTTTCAAACCAGATCTCACTTTGGAAGAGGTACAGGCAGAAAATCCCAAAGT  
GTCCAGAGGCCGGTATCGCCCTCAGGAATGTAAAGCTTTACAGAGGGTCGCCATCCTCGTTCC  
CCACCGGAACAGAGAGAAACACCTGATGTACCTGCTGGAACATCTGCATCCCTTCCTGCAGAG  
GCAGCAGCTGGATTATGGCATCTACGTCATCCACCAGGCTGAAGGTAAAAAGTTTAATCGAGC  
CAAACCTCTTGAATGTGGGCTATCTAGAAGCCCTCAAGGAAGAAAATTGGGACTGCTTTATATT  
CCACGATGTGGACCTGGTACCCGAGAATGACTTTAACCTTTACAAGTGTGAGGAGCATCCCCAA  
GCATCTGGTGGTTGGCAGGAACAGCACTGGGTACAGGTTACGTTACAGTGGAATTTTTGGGGG  
TGTTACTGCCCTAAGCAGAGAGCAGTTTTTCAAGGTGAATGGATTCTCTAACAACCTACTGGGG  
ATGGGGAGGCGAAGACGATGACCTCAGACTCAGGGTTGAGCTCCAAAGAATGAAAATTTCCCG  
GCCCCTGCCTGAAGTGGGTAAATATACAATGGTCTTCCACACTAGAGACAAAGGCAATGAGGT  
GAACGCAGAACGGATGAAGCTCTTACACCAAGTGTACAGAGTCTGGAGAACAGATGGGTTGAG  
TAGTTGTTCTTATAAATTAGTATCTGTGGAACACAATCCTTTATATATCAACATCACAGTGGA  
TTTCTGGTTTGGTGCATTGACCCTGGATCTTTTGGTGATGTTTGGGAAGAACTGATTCTTTGTTT  
GCAATAATTTTGGCCTAGAGACTTCAAATAGTAGCACACATTAAGAACCTGTTACAGCTCATT  
GTTGAGCTGAATTTTTCTTTTTGTATTTTCTTAGCAGAGCTCCTGGTGATGTAGAGTATAAA  
ACAGTTGTAACAAGACAGCTTTCTTAGTCATTTTGTATCATGAGGGTTAAATATTGTAATATGG  
ATACTTGAAGGACTTTATATAAAAGGATGACTCAAAGGATAAAATGAACGCTATTTGAGGACT  
CTGGTTGAAGGAGATTTATTTAAATTTGAAGTAATATATTATGGGATAAAAGGCCACAGGAAA  
TAAGACTGCTGAATGTCTGAGAGAACCAGAGTTGTTCTCGTCCAAGGTAGAAAGGTACGAAGA  
TACAATACTGTTATTTCATTTATCCTGTACAATCATCTGTGAAGTGGTGGTGTGAGGTGAGAAG  
GCGTCCACAAAAGAGGGGAGAAAAGGCGACGAATCAGGACACAGTGAACCTGGGAATGAAGAG  
GTAGCAGGAGGGTGGAGTGTGCGCTGCAAAGGCAGCAGTAGCTGAGCTGGTTGCAGGTGCTGA  
TAGCCTTCAGGGGAGGACCTGCCAGGTATGCCTTCCAGTGATGCCACCAGAGAATACATTC  
TCTATTAGTTTTTAAAGAGTTTTTGTAATAATGATTTTGTACAAGTAGGATATGAATTAGCAGT  
TTACAAGTTTACATATTAATAATAATAATATGTCTATCAAATACCTCTGTAGTAAAATGTG  
AAAAAGCAAAA

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**FIGURE 42**

MGFNLT FHL SYKFRLLLLL TLCLTVVGWATS NYFVGAIQEIPKAKEFMANFHKTLILGKGKTL  
TNEASTKKVELDNCPSVSPYLRGQSKLIFKPDLTLEEVQAENPKVSRGRYRPQECKALQRVAI  
LVPHRNREKHLMYLLEHLHPFLQRQQLDYGIYVIHQAEKKFNRAKLLNVGYLEALKEENWDC  
FIFHDVDLVPENDFNLYKCEEHPKHLVVGRNSTGYRLRYSGYFGGVTA LSREQFFKVNGFSNN  
YWG WGGEDDDLRLRVELQRMKISRPLPEVGKYTMVFHTRDKGNEVNAERMKLLHQVSRVWRD  
GLSSCSYKLVSVEHNPLYINITVDFWFGA

**Important features:****Signal peptide:**

amino acids 1-27

**N-glycosylation sites.**

amino acids 4-8, 220-224, 335-339

**Xylose isomerase proteins.**

amino acids 191-202



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**FIGURE 44**

MALSSQIWAACLLLLLLLLASLTSGSVFPQQTGQLAELQPQDRAGARASWMPMFQRRRRRDTHF  
PICIFCCGCCHRSKCGMCCKT

**Important features:****Signal peptide:**

amino acids 1-24

**cAMP- and cGMP-dependent protein kinase phosphorylation site.**

amino acids 58-59

**N-myristoylation site.**

amino acids 44-50

**Prokaryotic membrane lipoprotein lipid attachment site.**

amino acids 1-12

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**FIGURE 45**

GTGGCTTCATTTTCAGTGGCTGACTTCCAGAGAGCAATATGGCTGGTTCCCCAACATGCCTCAC  
CCTCATCTATATCCTTTGGCAGCTCACAGGGTCAGCAGCCTCTGGACCCGTGAAAGAGCTGGT  
CGGTTCCGTTGGTGGGGCCGTGACTTTCCCCCTGAAGTCCAAAGTAAAGCAAGTTGACTCTAT  
TGTCTGGACCTTCAACACAACCCCTCTTGTCAACATACAGCCAGAAGGGGGCACTATCATAGT  
GACCCAAAATCGTAATAGGGAGAGAGTAGACTTCCCAGATGGAGGCTACTCCCTGAAGCTCAG  
CAAACCTGAAGAAGAATGACTCAGGGATCTACTATGTGGGGATATACAGCTCATCACTCCAGCA  
GCCCTCCACCCAGGAGTACGTGCTGCATGTCTACGAGCACCTGTCAAAGCCTAAAGTCACCAT  
GGGTCTGCAGAGCAATAAGAATGGCACCTGTGTGACCAATCTGACATGCTGCATGGAACATGG  
GGAAGAGGATGTGATTTATACCTGGAAGGCCCTGGGGCAAGCAGCCAATGAGTCCCATAATGG  
GTCCATCCTCCCCATCTCCTGGAGATGGGGAGAAAGTGATATGACCTTCATCTGCGTTGCCAG  
GAACCCTGTCAGCAGAACTTCTCAAGCCCCATCCTTGCCAGGAAGCTCTGTGAAGGTGCTGC  
TGATGACCCAGATTCTCCATGGTCCTCCTGTGTCTCCTGTTGGTGCCCTCCTGCTCAGTCT  
CTTTGTACTGGGGCTATTTCTTTGGTTTCTGAAGAGAGAGAGACAAGAAGAGTACATTGAAGA  
GAAGAAGAGAGTGGACATTTGTCGGGAACTCCTAACATATGCCCCATTCTGGAGAGAACAC  
AGAGTACGACACAATCCCTCACACTAATAGAACAATCCTAAAGGAAGATCCAGCAAATACGGT  
TTACTCCACTGTGGAAATACCGAAAAAGATGGAAAATCCCCACTCACTGCTCACGATGCCAGA  
CACACCAAGGCTATTTGCCTATGAGAATGTTATCTAGACAGCAGTGCCTCCCCTAAGTCTCT  
GCTCA

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**FIGURE 46**

MAGSPTCLTLIYILWQLTGSAAAGPVKELVGSVGGAVTFPLKSKVKQVDSIVWTFNTTPLVTI  
QPEGGTIIVTQNRNRERVDFFPDGGYSLKLSKLKKNDSGIYYVGIYSSSLQQPSTQEYVLHVYE  
HLSKPKVTMGLQSNKNGTCVTNLTCCMEHGEEVDIYTWKALGQAANESHNGSILPISWRWGES  
DMTFICVARNPVSRNFSSPILARKLCEGAADDPDSSMVLLCLLLVPLLLSLFVLGLFLWFLKR  
ERQEEYIEEKKRVDICRETPNICPHSGENTYDTIPHTNRTILKEDPANTVYSTVEIPKKMEN  
PHSLLTMPDTPRLFAYENVI

**Important features:****Signal peptide:**

amino acids 1-22

**Transmembrane domain:**

amino acids 224-250

**Leucine zipper pattern.**

amino acids 229-251

**N-glycosylation sites.**amino acids 98-102, 142-146, 148-152, 172-176, 176-180, 204-208,  
291-295



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**FIGURE 47**

GGCTCGAGCGTTTCTGAGCCAGGGGTGACCATGACCTGCTGCGAAGGATGGACATCCTGCAAT  
GGATTTCAGCCTGCTGGTTCTACTGCTGTTAGGAGTAGTTCTCAATGCGATACCTCTAATTGTC  
AGCTTAGTTGAGGAAGACCAATTTTCTCAAAACCCCATCTCTTGCTTTGAGTGGTGGTTCCCA  
GGAATTATAGGAGCAGGTCTGATGGCCATTCCAGCAACAACAATGTCCTTGACAGCAAGAAAA  
AGAGCGTGCTGCAACAACAGAACTGGAATGTTTCTTTCATCATTTTTTCAGTGTGATCACAGTC  
ATTGGTGCTCTGTATTGCATGCTGATATCCATCCAGGCTCTCTTAAAAGGTCCTCTCATGTGT  
AATTCTCCAAGCAACAGTAATGCCAATTGTGAATTTTCATTGAAAAACATCAGTGACATTCAT  
CCAGAATCCTTCAACTTGCAGTGGTTTTTCAATGACTCTTGTGCACCTCCTACTGGTTTTCAAT  
AAACCCACCAGTAACGACACCATGGCGAGTGGCTGGAGAGCATCTAGTTTCCACTTCGATTCT  
GAAGAAAACAAACATAGGCTTATCCACTTCTCAGTATTTTTAGGTCTATTGCTTGTTGGAATT  
CTGGAGGTCCTGTTTGGGCTCAGTCAGATAGTCATCGGTTTCCTTGGCTGCTCTGTGTGGAGTC  
TCTAAGCGAAGAAGTCAAATTGTGTAGTTTAATGGGAATAAAATGTAAGTATCAGTAGTTTGA  
AAAAAAAAA

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**FIGURE 48**

MTCCEGWTSCNGFSLLVLLLLGVVLNAIPLIVSLVEEDQFSQNPISCFEWWFPGIIGAGLMAI  
PATMTSLTARKRACCNNRTGMFLSSFFSVITVIGALYCM LISIQALLKGPLMCNSPSNSNANC  
EFSLKNISDIHPESFNLQWFFNDSCAPPTGFNKPTSNDTMASGWRASSFHFDSEENKHRLIHF  
SVFLGLLLVGILEVLFGLSQIVIGFLGCLCGVSKRRSQIV

**Important features:****Transmembrane domains:**

amino acids 10-31 (type II), 50-72, 87-110, 191-213

**N-glycosylation sites.**

amino acids 80-84, 132-136, 148-152, 163-167

**cAMP- and cGMP-dependent protein kinase phosphorylation site.**

amino acids 223-227

**N-myristoylation sites.**

amino acids 22-28, 54-60, 83-89, 97-103, 216-222

**Prokaryotic membrane lipoprotein lipid attachment site.**

amino acids 207-218

**TNFR/NGFR family cysteine-rich region protein.**

amino acids 4-12

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**FIGURE 49**

ATCCGTTCTCTGCGCTGCCAGCTCAGGTGAGCCCTCGCCAAGGTGACCTCGCAGGACACTGGT  
GAAGGAGCAGTGAGGAACCTGCAGAGTCACACAGTTGCTGACCAATTGAGCTGTGAGCCCTGGA  
GCAGATCCGTGGGCTGCAGACCCCGCCCCAGTGCCTCTCCCCCTGCAGCCCTGCCCCCTCGAA  
CTGTGACATGGAGAGAGTGACCCTGGCCCTTCTCCTACTGGCAGGCCTGACTGCCTTGGAAGC  
CAATGACCCATTTGCCAATAAAGACGATCCCTTCTACTATGACTGGAAAAACCTGCAGCTGAG  
CGGACTGATCTGCGGAGGGCTCCTGGCCATTGCTGGGATCGCGGCAGTTCTGAGTGGCAAATG  
CAAATACAAGAGCAGCCAGAAGCAGCACAGTCCTGTACCTGAGAAGGCCATCCCACATCAC  
TCCAGGCTCTGCCACTACTTGCTTGAGCACAGGACTGGCCTCCAGGGATGGCCTGAAGCCTAAC  
ACTGGCCCCCAGCACCTCCTCCCCCTGGGAGGCCTTATCCTCAAGGAAGGACTTCTCTCCAAGG  
GCAGGCTGTTAGGCCCCCTTTCTGATCAGGAGGCTTCTTTATGAATTAACTCGCCCCACCACC  
CCCTCA

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## **FIGURE 50**

MERVTLALLLLAGLTALEANDPFANKDDPFYYDWKNLQLSGLICGGLLAIAGIAAVLSGKCKY  
KSSQKQHSPVPEKAIPITPGSATTC

**Important features:**

**Signal peptide:**

amino acids 1-16

**Transmembrane domain:**

amino acids 36-59

**N-myristoylation sites.**

amino acids 41-47, 45-51, 84-90

**Extracellular proteins SCP/Tpx-1/Ag5/PR-1/Sc7.**

amino acids 54-67

[illegible]

**FIGURE 52**

amino acids 301-304

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**FIGURE 53**

GGAGAAGAGGTTGTGTGGGACAAGCTGCTCCCGACAGAAGGATGTCGCTGCTGAGCCTGCCCT  
GGCTGGGCCTCAGACCGGTGGCAATGTCCCCATGGCTACTCCTGCTGCTGGTGTGGGCTCCT  
GGCTACTCGCCCGCATCCTGGCTTGGACCTATGCCTTCTATAACAACCTGCCGCCGGCTCCAGT  
GTTTCCCACAGCCCCCAAACGGAACTGGTTTTTGGGGTCACCTGGGCCTGATCACTCCTACAG  
AGGAGGGCTTGAAGGACTCGACCCAGATGTCGGCCACCTATTCCCAGGGCTTTACGGTATGGC  
TGGGTCCCATCATCCCCTTCATCGTTTTATGCCACCCTGACACCATCCGGTCTATACCAATG  
CCTCAGCTGCCATTGCACCCAAGGATAATCTCTTCATCAGGTTCTTGAAGCCCTGGCTGGGAG  
AAGGGATACTGCTGAGTGGCGGTGACAAGTGGAGCCGCCACCGTCGGATGCTGACGCCCGCCT  
TCCATTTCAACATCCTGAAGTCCTATATAACGATCTTCAACAAGAGTGCAAACATCATGCTTG  
ACAAGTGGCAGCACCTGGCCTCAGAGGGCAGCAGTCGTCTGGACATGTTTGAGCACATCAGCC  
TCATGACCTTGGACAGTCTACAGAAATGCATCTTCAGCTTTGACAGCCATTGTCAGGAGAGGC  
CCAGTGAATATATTGCCACCATCTTGGAGCTCAGTGCCCTTGTTAGAGAAAAGAAGCCAGCATA  
TCCTCCAGCACATGGACTTTCTGTATTACCTCTCCCATGACGGGCGGCGCTTCCACAGGGCCT  
GCCGCCTGGTGATGACTTCACAGACGCTGTATCCGGGAGCGGCGTTCGACCCCTCCCCACTC  
AGGGTATTGATGATTTTTTCAAAGACAAAGCCAAGTCCAAGACTTTGGATTTCAATTGATGTGC  
TTCTGCTGAGCAAGGATGAAGATGGGAAGGCATTGTCTAGATGAGGATATAAGAGCAGAGGCTG  
ACACCTTCATGTTTGGAGGCCATGACACCACGGCCAGTGGCCTCTCCTGGGTCTGTACAACC  
TTGCGAGGCACCCAGAATACCAGGAGCGCTGCCGACAGGAGGTGCAAGAGCTTCTGAAGGACC  
GCGATCCTAAAGAGATTGAATGGGACGACCTGGCCCAGCTGCCCTTCCTGACCATGTGCGTGA  
AGGAGAGCCTGAGGTTACATCCCCCAGCTCCCTTCATCTCCCGATGCTGCACCCAGGACATTG  
TTCTCCCAGATGGCCGAGTCATCCCCAAAGGCATTACCTGCCTCATCGATATTATAGGGGTCC  
ATCACAACCCAACTGTGTGGCCGGATCCTGAGGTCTACGACCCCTTCCGCTTTGACCCAGAGA  
ACAGCAAGGGGAGGTCACCTCTGGCTTTTATTCTTTCTCCGCAGGGCCCAGGAACTGCATCG  
GGCAGGCGTTCCGCATGGCGGAGATGAAAGTGGTCCTGGCGTTGATGCTGCTGCACTTCCGGT  
TCCTGCCAGACCACACTGAGCCCCGCAGGAAGCTGGAATTGATCATGCGCGCCGAGGGCGGGC  
TTTGGCTGCGGGTGGAGCCCCTGAATGTAGGCTTGCAAGTGAATTTCTGACCCATCCACCTGTT  
TTTTTGCAGATTGTCTATGAATAAAACGGTGCTGTCAAA

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**FIGURE 54**

MSLLSLPWLGLRPVAMSPWLLLLLVVGSWLLARILAWTYAFYNNCRRLQCFPPKRNWFWGH  
LGLITPTEEGLDKSTQMSATYSQGF<sup>T</sup>VWLGP<sup>I</sup>IPFIVLCHPDTIRSITNASAAIAPKDNLFIR  
FLKPWLGE<sup>G</sup>ILLSGGDKWSRHRRLTPAFHFNILKSYITIFNKSANIMLDKWQHLASEGSSRL  
DMFEHISLMTLDSLQKCIFSFD<sup>S</sup>HCQERPSEYIATILELSALVEKRSQHILQHMDFLYYLSHD  
GRRFHRACRLVHDFTDAVIRERRRTLPTQ<sup>G</sup>IDDFFKDKAKSKTLD<sup>F</sup>IDVLLLSKDE<sup>D</sup>GKALS<sup>D</sup>  
EDIRAEADTFMFGGHDTTASGLSWVLYNLARHPEYQERCRQEVQELLKDRDPKEIEWDDLAQL  
PFLTMCVKESRLHPPAPFISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNPTVWPDPEVYD  
PFRFDPENSKGRSPLAFIPFSAGPRNCIGQAFAMAEMKVVLALMLLHFRFLPDHTEPRRKLEL  
IMRAEGGLWLRVEPLNVGLQ

**Important features:****Transmembrane domains:**

amino acids 13-32 (type II), 77-102

**Cytochrome P450 cysteine heme-iron ligand signature.**

amino acids 461-471

**N-glycosylation sites.**

amino acids 112-116, 168-172



**FIGURE 55**

[illegible]

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## **FIGURE 56**

MGPVKQLKRMFEPTRLIATIMVLLCFALTLCSAFWWHNKGLALIFCILQSLALTWYSLSFIPF  
ARDAVKKCFVCLA

**Important features:**

**Signal peptide:**

amino acids 1-33

**Type II fibronectin collagen-binding domain protein.**

amino acids 30-72

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**FIGURE 57**

CGGCTCGAGCTCGAGCCGAATCGGCTCGAGGGGAGTGGAGCACCCAGCAGGCCGCCAACATGCTCTGTCTGTGC  
CTGTACGTGCCGGTTCATCGGGGAAGCCAGACCGAGTTCCAGTACTTTGAGTCGAAGGGGCTCCCTGCCGAGCTG  
AAGTCCATTTTCAAGCTCAGTGTCTTCATCCCCCTCCAGGAATTCTCCACCTACCGCCAGTGGGAAGCAGAAAATT  
GTACAAGCTGGAGATAAGGACCTTGATGGGCAGCTAGACTTTGAAGAATTTGTCCATTATCTCCAAGATCATGAG  
AAGAAGCTGAGGCTGGTGTTTAAGATTTTGGACAAAAAAGATGATGGACGCATTGACGCGCAGGAGATCATGCAG  
TCCCTGCGGGACTTGGGAGTCAAGATATCTGAACAGCAGGCAGAAAAAATTCTCAAGAGCATGGATAAAAAACGGC  
ACGATGACCATCGACTGGAACGAGTGGAGAGACTACCACCTCCTCCACCCCGTGGAAAAACATCCCCGAGATCATC  
CTCTACTGGAAGCATTCACGATCTTTGATGTGGGTGAGAATCTAACGGTCCCGGATGAGTTCACAGTGGAGGAG  
AGGCAGACGGGGATGTGGTGGAGACACCTGGTGGCAGGAGGTGGGGCAGGGGGCGTATCCAGAACCTGCACGGCC  
CCCCGGACAGGCTCAAGGTGCTCATGCAGGTCCATGCCTCCCGCAGCAACAACATGGGCATCGTTGGTGGCTTC  
ACTCAGATGATTCGAGAAGGAGGGGCCAGGTCACTCTGGCGGGCAATGGCATCAACGTCCTCAAAATTGCCCCC  
GAATCAGCCATCAAAATTCATGGCTATGAGCAGATCAAGCGCTTGTGGTAGTGACCAGGAGACTCTGAGGATT  
CACGAGAGGCTTGTGGCAGGGTCTTGGCAGGGGCCATCGCCCAGAGCAGCATCTACCCAATGGAGGTCTGGAAG  
ACCCGATGGCGCTGCGGAAGACAGGCCAGTACTCAGGAATGCTGGACTGCGCCAGGAGGATCTGGCCAGAGAG  
GGGTGGCCCGCTTCTACAAAGGCTATGTCCCAACATGCTGGGCATCATCCCCCTATGCCGGCATCGACCTTGCA  
GTCTACGAGACGCTCAAGAATGCCTGGCTGCAGCACTATGCAGTGAACAGCGCGGACCCCGCGTGTGTGTCTC  
CTGGCTGTGGCACCATGTCCAGTACCTGTGGCAGCTGGCCAGCTACCCCTGGCCCTAGTCAGGACCCGGATG  
CAGGCGCAAGCCTCTATTGAGGGCGCTCCGGAGGTGACCATGAGCAGCCTCTTCAAAACATATCTGCGGACCGAG  
GGGGCTTCGGGCTGTACAGGGGGCTGGCCCCAACTTCATGAAGGTATCCAGCTGTGAGCATCAGTACGTG  
GTCTACGAGAACCTGAAGATCACCTGGGCGTGCAGTGCAGGTGACCGGGTGAACGGGGGAGGGCCGCCCGCATCG  
CTGATCCTGGGCGCAGCCTGGGGTGTGCAGCCATCTCATTCTGTGAATGTGCCAACACTAAGCTGTCTCGAGCC  
AAGCTGTGAAAACCTAGACGCACCCGAGGGAGGGTGGGGAGAGCTGGCAGGCCAGGGCTTGTCTGTCTGACC  
CCAGCAGACCTCCTGTGGTTCAGCGAAGACCACAGGCATTCCTTAGGGTCCAGGGTCAGCAGGCTCCGGGCT  
CACATGTGTAAGGACAGGACATTTCTGCAGTGCCTGCCAATAGTGAGCTTGGAGCCTGGAGGCCGGCTTAGTTT  
TTCCATTTTACCTTGCAGCCAGCTGTGGCCACGGCCCCCTGCCCTCTGGTCTGCCGTGCATCTCCCTGTGGCTC  
CTTGCTGCCTGCCTGTCTGCTGAGGTAAGGTGGGAGGAGGGCTACAGCCACATCCCACCCCTCGTCCAATCCC  
ATAATCCATGATGAAAGGTGAGGTACGTGGCTCCAGGCCGACTTCCCAACCTACAGCATTGAGGCCAACTT  
GGCTGTGAAGGAAGAGGAAGGATCTGGCCTTGTGGTCACTGGCATCTGAGCCCTGCTGATGGCTGGGGCTCTCG  
GGCATGCTTGGGAGTGCAGGGGGCTCGGGCTGCCCTGGCTGCACAGAAGGCAAGTGTGGGGCTCATGGTG  
CTCTGAGCTGGCTGGACCCTGTGAGGATGGGCCCCACCTCAGAACCAAACTCACTGTCCCCACTGTGGCATGAG  
GGCAGTGGAGCACCATGTTTGAAGGCGAAGGGCAGAGCGTTTGTGTGTTCTGGGAGGGAAGGAAAAGGTGTTGG  
AGGCCCTAATTATGACTGTTGGGAAAAGGGTTTGTCCAGAAGGACAAGCCGGACAAATGAGCGACTTCTGTGC  
TTCCAGAGGAAGACGAGGGAGCAGGAGCTTGGCTGACTGCTCAGAGTCTGTTCTGACGCCCTGGGGGTTCCTGTC  
CAACCCAGCAGGGGCGCAGCGGACCCAGCCACACTTGTGTCACTGCTTGGAACTATTTATTTTGTGTA  
TTTTATTGAACAGAGTTATGTCTAACTATTTTATAGATTTGTTAATTAATAGCTTGTCAATTTCAAGTTCAT  
TTTTTATTATATTTATGTTTATGTTTACCTTCCCAAGCCCGCCAGTGGGATGGGAGGAGGAGGAGAA  
GGGGGGCTTGGGGCGCTGCAGTACATCTGTCCAGAGAAATTCCTTTTGGGACTGGAGGCAGAAAAGCGGCCAG  
AAGGCAGCAGCCCTGGCTCCTTTCTTGGCAGGTTGGGGAAGGGCTTGGCCCCAGCCTTAGGATTTCAAGGTTT  
GACTGGGGGCGTGGAGAGAGAGGGAGGAACCTCAATAACCTGAAGGTGGAATCCAGTTATTTCTGCGCTCGCA  
GGGTTTCTTTATTTCACTCTTTTCTGAATGTCAAGGCAGTGAGGTGCCTCTCACTGTGAATTTGTGGTGGGCGGG  
GGCTGGAGGAGAGGGTGGGGGGCTGGCTCCGTCCTCCAGCCTTCTGCTGCCCTTGCTTAACAATGCCGGCCAA  
CTGGCGACCTCACGTTGCACTTCCATTCCACCAGAATGACCTGATGAGGAAATCTCAATAGGATGCAAAGATC  
AATGCAAAAATTGTTATATATGAACATATAACTGGAGTCTGCAAAAAGCAAATTAAGAAAGAATTGGACGTTAGA  
AGTTGTCAATTTAAAGCAGCCTTCTAATAAAGTTGTTTCAAAGCTGAAAAAAGGAAAAAAGGAAAAAAGG  
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 58**

MLCLCLYVPVIGEATFQYFESKGLPAELKSIFKLSVFIPSQEFSTYRQWKQKIVQAGDKDL  
DGQLDFEEFVHYLQDHEKKLRLVFKILDKKNDGRIDAQEIMQSLRDLGVKISEQQAEEKILKSM  
DKNGTMTIDWNEWRDYHLLHPVENIPEIILYWKHSTIFDVGENLTVPDEFTVEERQTGMWWRH  
LVAGGGAGAVSRTCTAPLDRLKVLMOVHASRSNNMGIVGGFTQMIREGGARSLWRGNGINVLK  
IAPESAIKFMAYEQIKRLVGSDQETLRIHERLVAGSLAGAIAQSSIYPMEVLKTRMALRKTGQ  
YSGMLDCARRILAREGVAAFYKGYVPNMLGIIIPYAGIDLAVYETLKNAWLQHYAVNSADPGVF  
VLLACGTMSSTCGQLASYPLALVRTRMQAQAASIEGAPEVTMSSLFKHILRTEGAFLYRGLAP  
NFMKVIPAVSISYVVYENLKITLGVQSR

**Important features:****Signal peptide:**

amino acids 1-16

**Putative transmembrane domains:**

amino acids 284-304, 339-360, 376-394

**Mitochondrial energy transfer proteins signature.**

amino acids 206-215, 300-309

**N-glycosylation sites.**

amino acids 129-133, 169-173

**Elongation Factor-hand calcium-binding protein.**

amino acids 54-73, 85-104, 121-140



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**FIGURE 60**

MASLGQILFWSIISIISIIILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDIK  
LSDIVIQWLKEGVLGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNVQLTDAG  
TYKCYIITSKGKGNANLEYKTGAFSMPEVNVDYNASSETLRCEAPRWFPOPTVWVASQVDQGA  
NFSEVSNTSFELNSENVTMKVVSVLYNVTINNTYSCMIENDIAKATGDIKVTESI KRRSHLQ  
LLNSKASLCVSSFFAISWALLPLSPYMLK

**Important features:****Signal peptide:**

amino acids 1-28

**Transmembrane domain:**

amino acids 258-281

**N-glycosylation sites.**amino acids 112-116, 160-164, 190-194, 196-200, 205-209, 216-220,  
220-224**N-myristoylation sites.**

amino acids 52-58, 126-132, 188-194

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**FIGURE 61**

TGACGTCAGAATCACC**ATG**GCCAGCTATCCTTACCGGCAGGGCTGCCCAGGAGCTGCAGGACA  
AGCACCAGGAGCCCCCTCCGGGTAGCTACTACCCTGGACCCCCCAATAGTGGAGGGCAGTATGG  
TAGTGGGCTACCCCCCTGGTGGTGGTTATGGGGGTCCTGCCCCCTGGAGGGCCTTATGGACCACC  
AGCTGGTGGAGGGCCCTATGGACACCCCAATCCTGGGATGTTCCCCCTCTGGA ACTCCAGGAGG  
ACCATATGGCGGTGCAGCTCCCGGGGGCCCCCTATGGTCAGCCACCTCCAAGTTCCTACGGTGC  
CCAGCAGCCTGGGCTTTATGGACAGGGTGGCGCCCCCTCCCAATGTGGATCCTGAGGCCTACTC  
CTGGTTCCAGTCGGTGGACTCAGATCACAGTGGCTATATCTCCATGAAGGAGCTAAAGCAGGC  
CCTGGTCAACTGCAATTGGTCTTCATTCAATGATGAGACCTGCCTCATGATGATAAACATGTT  
TGACAAGACCAAGTCAGGCCGCATCGATGTCTACGGCTTCTCAGCCCTGTGGAAATTCATCCA  
GCAGTGGGAAGAACCTCTTCCAGCAGTATGACCGGGACCGCTCGGGCTCCATTAGCTACACAGA  
GCTGCAGCAAGCTCTGTCCCAAATGGGCTACAACCTGAGCCCCAGTTCACCCAGCTTCTGGT  
CTCCCGCTACTGCCACGCTCTGCCAATCCTGCCATGCAGCTTGACCGCTTCATCCAGGTGTG  
CACCCAGCTGCAGGTGCTGACAGAGGCCTTCCGGGAGAAGGACACAGCTGTACAAGGCAACAT  
CCGGCTCAGCTTCGAGGACTTCGTCACCATGACAGCTTCTCGGATGCTAT**TGA**CCCAACCATCT  
GTGGAGAGTGGAGTGCACCAGGGACCTTTCTGGCTTCTTAGAGTGAGAGAAGTATGTGGACA  
TCTCTTCTTTTCTGTCCCTCTAGAAGAACATTCTCCCTTGCTTGATGCAACACTGTTCCAAA  
AGAGGGTGGAGAGTCCTGCATCATAGCCACCAAATAGTGAGGACCGGGGCTGAGGCCACACAG  
ATAGGGGCCTGATGGAGGAGAGGATAGAAGTTGAATGTCCTGATGGCCATGAGCAGTTGAGTG  
GCACAGCCTGGCACCAGGAGCAGGTCCTTGTAATGGAGTTAGTGTCCAGTCAGCTGAGCTCCA  
CCCTGATGCCAGTGGTGAGTGTTTCATCGGCCTGTTACCGTTAGTACCTGTGTTCCCTCACCAG  
GCCATCCTGTCAAACGAGCCCATTTTCTCCAAAGTGGAATCTGACCAAGCATGAGAGAGATCT  
GTCTATGGGACCAGTGGCTTGGATTCTGCCACACCCATAAATCCTTGTGTGTTAACTTCTAGC  
TGCTGGGGCTGGCCCTGCTCAGACAAATCTGCTCCCTGGGCATCTTTGGCCAGGCTTCTGCC  
CCCTGCAGCTGGGACCCCTCACTTGCCTGCCATGCTCTGCTCGGCTTCAGTCTCCAGGAGACA  
GTGGTCACCTCTCCCTGCCAATACTTTTTTTAATTTGCATTTTTTTTCATTTGGGGCCAAAAG  
TCCAGTGAAATTGTAAGCTTCAATAAAAGGATGAAACTCTGA

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**FIGURE 62**

MASYPYRQGCPGAAGQAPGAPPGSYYPGPPNSGGQYGSGLPPGGGYGGPAPGGPYGPPAGGGP  
YGHNPNGMFPSGTPGGPYGGAAPGGPYGQPPSSYGAQQPGLYGQGGAPPNVDPEAYSWFQSV  
DSDHSGYISMKELKQALVNCNWSSFNDCTCLMMINMFDKTKSGRIDVYGFSALWKFIQQWKNL  
FQQYDRDRSGSISYTELQQALSQMGYNLSPQFTQLLVSRYCPRSANPAMQLDRFIQVCTQLQV  
LTEAFREKDTAVQGNIRLSFEDEVMTMTASRML

**Important features of the protein:****Signal peptide:**

amino acids 1-19

**N-glycosylation site.**

amino acids 147-150

**Casein kinase II phosphorylation sites.**

amino acids 135-138, 150-153, 202-205, 271-274

**N-myristoylation sites.**amino acids 9-14, 15-20, 19-24, 33-38, 34-39, 39-44, 43-48, 61-  
66, 70-75, 78-83, 83-88, 87-92, 110-115



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**FIGURE 63**

CAGGATGCAGGGCCGCGTGGCAGGGAGCTGCGCTCCTCTGGGCCTGCTCCTGGTCTGTCTTCA  
TCTCCCAGGCCTCTTTGCCCCGAGCATCGGTGTTGTGGAGGAGAAAGTTTCCCAAACTTCGG  
GACCAACTTGCCTCAGCTCGGACAACCTTCCTCCACTGGCCCCCTCTAACTCTGAACATCCGCA  
GCCCCTCTGGACCCTAGGTCTAATGACTTGGCAAGGGTTCCTCTGAAGCTCAGCGTGCCTCC  
ATCAGATGGCTTCCCACCTGCAGGAGGTTCTGCAGTGCAGAGGTGGCCTCCATCGTGGGGGCT  
GCCTGCCATGGATTCTTGGCCCCCTGAGGATCCTTGGCAGATGATGGCTGCTGCGGCTGAGGA  
CCGCCTGGGGGAAGCGCTGCCTGAAGAACTCTCTTACCTCTCCAGTGCTGCGGGCCCTCGCTCC  
GGGCAGTGGCCCTTTGCCTGGGGAGTCTTCTCCCGATGCCACAGGCCTCTCACCTGAGGCTTC  
ACTCCTCCACCAGGACTCGGAGTCCAGACGACTGCCCCGTTCTAATTCAGTGGGAGCCGGGGG  
AAAAATCCTTTCCCAACGCCCTCCCTGGTCTCTCATCCACAGGGTTCTGCCTGATCACCCCTG  
GGGTACCCTGAATCCCAGTGTGTCTTGGGGAGGTGGAGGCCCTGGGACTGGTTGGGGAACGAG  
GCCCATGCCACACCCTGAGGGAATCTGGGGTATCAATAATCAACCCCCAGGTACCAGCTGGGG  
AAATATTAATCGGTATCCAGGAGGCAGCTGGGGAAATATTAATCGGTATCCAGGAGGCAGCTG  
GGGGAATATTAATCGGTATCCAGGAGGCAGCTGGGGGAATATTCATCTATACCCAGGTATCAA  
TAACCCATTTCTCCTGGAGTTCTCCGCCCTCCTGGCTCTTCTTGGAACATCCCAGCTGGCTT  
CCCTAATCCTCCAAGCCCTAGGTTGCAGTGGGGCTTAGAGCACGATAGAGGGAAACCCAACATT  
GGGAGTTAGAGTCCTGCTCCCGCCCCCTTGCTGTGTGGGCTCAATCCAGGCCCTGTTAACATGT  
TTCCAGCACTATCCCCACTTTTCAGTGCCTCCCCTGCTCATCTCCAATAAAATAAAAGCACTT  
ATGAAA  
AAA

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**FIGURE 64**

MQGRVAGSCAPLGLLLVCLHLPGLFARSIGVVEEKVSQNFGTNLPQLGQPSSTGSPNSEHPQP  
ALDPRSNDLARVPLKLSVPPSDGFPPAGGS AVQRWPPSWGLPAMDSWPPEDPWQMMAAAAEDR  
LGEALPEELSYLSSAAALAPGSGPLPGESSPDATGLSPEASLLHQDSESRRRLPRSNSLGAGGK  
ILSQRPPWSLIHRVLPDHPWGTLNPSVSWGGGGPGTGWGTRPMPHPEGIWGINNQPPGTSGWN  
INRYPGGSWGNINRYPGGSWGNINRYPGGSWGNIHLYPGINNPFPPGVLRPPGSSWNIPAGFP  
NPPSPRLQWG

**Important features of the protein:****Signal peptide:**

amino acids 1-26

**Casein kinase II phosphorylation sites.**

amino acids 56-59, 155-158

**N-myristoylation sites.**amino acids 48-53, 220-225, 221-226, 224-229, 247-252, 258-263,  
259-264, 269-274, 270-275, 280-285, 281-286, 305-310

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**FIGURE 65**

AAGGAGAGGCCACCGGGACTTCAGTGTCTCCTCCATCCCAGGAGCGCAGTGGCCACTATGGGG  
TCTGGGCTGCCCCCTTGTCTCCTCTTGACCCCTCCTTGGCAGCTCACATGGAACAGGGCCGGGT  
ATGACTTTGCAACTGAAGCTGAAGGAGTCTTTTCTGACAAATTCCTCCTATGAGTCCAGCTTC  
CTGGAATTGCTTGAAAAGCTCTGCCTCCTCCTCCATCTCCCTTCAGGGACCAGCGTCACCCTC  
CACCATGCAAGATCTCAACACCATGTTGTCTGCAACACATTGACAGCCATTGAAGCCTGTGTCC  
TTCTTGGCCCGGGCTTTTGGGCCGGGGATGCAGGAGGCAGGCCCCGACCCTGTCTTTTCAGCAG  
GCCCCACCCTCCTGAGTGGCAATAAATAAAATTCGGTATGCTG

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## **FIGURE 66**

MGSGPLPLVLLLTLLGSSHGTGPGMTLQKLKESFLTNSSESSFLELLEKLCLLLHLPSTSV  
TLHHARSQHHVVCNT

**Important features:**

**Signal peptide:**

amino acids 1-19

**N-glycosylation site.**

amino acids 37-41

**N-myristoylation sites.**

amino acids 15-21, 19-25, 60-66

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**FIGURE 67**

ACGGACCGAGGGTTCGAGGGAGGGACACGGACCAGGAACCTGAGCTAGGTCAAAGACGCCCCGG  
GCCAGGTGCCCCGTCGCAGGTGCCCCCTGGCCGGAGATGCGGTAGGAGGGGCGAGCGCGAGAAG  
CCCCCTCCTCGGCGCTGCCAACCCGCCACCCAGCCCATGGCGAACCCCGGGCTGGGGCTGCTT  
CTGGCGCTGGGCCTGCCGTTCTGCTGGCCCCGCTGGGGCCGAGCCTGGGGGCAAATACAGACC  
ACTTCTGCAAATGAGAATAGCACTGTTTTGCCTTCATCCACCAGCTCCAGCTCCGATGGCAAC  
CTGCGTCCGGAAGCCATCACTGCTATCATCGTGGTCTTCTCCCTCTTGGCTGCCTTGCTCCTG  
GCTGTGGGGCTGGCACTGTTGGTGCGGAAGCTTCGGGAGAAGCGGCAGACGGAGGGCACCTAC  
CGGCCCAGTAGCGAGGAGCAGTTCTCCCATGCAGCCGAGGCCCGGGCCCCCTCAGGACTCCAAG  
GAGACGGTGCAGGGCTGCCTGCCCATCTAGGTCCCCTCTCCTGCATCTGTCTCCCTTCATTGC  
TGTGTGACCTTGGGGAAAGGCAGTGCCCTCTCTGGGCAGTCAGATCCACCCAGTGCTTAATAG  
CAGGGAAGAAGGTACTTCAAAGACTCTGCCCCTGAGGTCAAGAGAGGATGGGGCTATTCATT  
TTATATATTTATATAAAATTAGTAGTGAGATGTAAAAAAAAAAAAAAAAAAAA

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**FIGURE 68**

MANPGLGLLLALGLPFELLARWGRAWGQIQTTSANENSTVLPSSSTSSSSDGNLRPEAITAIIVV  
FSLLAALLLAVGLALLVRKLRQTEGTYRPSSEEQFSHAAEARAPQDSKETVQGCLPI

**Important features:****Signal peptide:**

amino acids 1-19

**Transmembrane domain:**

amino acids 56-80

**N-glycosylation site.**

amino acids 36-40

**cAMP- and cGMP-dependent protein kinase phosphorylation site.**

amino acids 86-90

**Tyrosine kinase phosphorylation site.**

amino acids 86-94

**N-myristoylation sites.**

amino acids 7-13, 26-32

[illegible]

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**FIGURE 70**

MGLFRGFVLLVLCLLHQSNSTFIKLNNNGFEDIVIVIDPSVPEDEKIIIEQIEDMVTTASTYL  
FEATEKRFFFKNVSILIPENWKENPQYKRPKHENHKKHADVIVAPPTLPGRDEPYTKQFTECGE  
KGEYIHFTPDLLLGKKQNEYGPPGKLFVHEWAHLRWGVFDEYNEDQPFYRAKSKKIEATRCSA  
GISGRNRVYKCQGGSCLSRACRIDSTTKLYGKDCQFFPDKVQTEKASIMFMQSIDSVVEFCNE  
KTHNQEAPSLQNIKCNFRSTWEVISNSEDFKNTIPMVTPPPPPVFSLKISQRIVCLVLDKSG  
SMGGKDRLNRMNQAAKHFLQTVENGSWVGMVHFDSTATIVNKLIQIKSSDERNTLMAGLPTY  
PLGGSICSIGIKYAFQVIGELHSQLDGSEVLLLT DGEDNTASSCIDEVKQSGAIVHFIALGRA  
ADEAVIEMSKITGGSHFYVSDEAQNNGLIDAFGALTSGNTDLSQKSLQLESKGLTLNSNAWMN  
DTVIIDSTVGKDTFFLITWNSLPPSISLWDPSTIMENFTVDATSKMAYLSIPGTAKVGTWAY  
NLQAKANPETLTITVTSRAANSSVPPITVNAKMNDVNSFPSPMIVYAEILQGYVPVLGANVT  
AFIESQNGHTEVLELLDNGAGADSEKNDGVYSRYFTAYTENGRYSLKVRAGGANTARLKL RP  
PLNRAAYIPGWVNGEIEANPPRPEIDEDTQT TLEDFSR TASGGAFVVSQVPSLPLPDQYPPS  
QITDL DATVHEDKIILTWTAPGDNFDVGKVQRYIIRISASILDLRDSFDDALQVNTTDLSPKE  
ANSKESFAFKPENISEENATHIFIAIKSIDKSNLTSKVS NIAQVTLFIPQANPDDIDPTPTPT  
PTPTPKSHNSGVNISTLVLSVIGSVVIVNFILSTTI

**Signal peptide:**

amino acids 1-21

**Putative transmembrane domains:**

amino acids 284-300, 617-633

**Leucine zipper pattern.**

amino acids 469-491, 476-498

**N-glycosylation site.**amino acids 20-24, 75-79, 340-344, 504-508, 542-546, 588-592,  
628-632, 811-815, 832-836, 837-841, 852-856, 896-900



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**FIGURE 71**

CTCCTTAGGTGGAAACCCTGGGAGTAGAGTACTGACAGCAAAGACCGGGAAAGACCATACGTCCCCGGGCAGGGG  
TGACAACAGGTGTCTCTTTTTGATCTCGTGTGTGGCTGCCTTCTTATTTCAAGGAAAGACGCCAAGGTAATTTT  
GACCCAGAGGAGCAATGATGTAGCCACCTCCTAACCTTCCCTTCTTGAACCCCCAGTTATGCCAGGATTTACTAG  
AGAGTGTCAACTCAACCAGCAAGCGGCTCCTTCGGCTTAACCTGTGGTTGGAGGAGAGAACCTTTGTGGGGCTGC  
GTTCTCTTAGCAGTGTCTCAGAAGTGACTTGCCTGAGGGTGGACCAGAAGAAAGGAAAGGTCCCCTCTTGCTGTTG  
GCTGCACATCAGGAAGGCTGTGATGGGAATGAAGGTGAAAACCTTGAGATTTCACTTCAGTCATTGCTTCTGCCT  
GCAAGATCATCTTTAAAGTAGAGAAGCTGCTCTGTGTGGTGGTTAACTCCAAGAGGCAGAACTCGTTCTAGAA  
GGAAATGGATGCAAGCAGCTCCGGGGGGCCCCAAACGCATGCTTCTGTGGTCTAGCCCAGGGAAGCCCTTCCGTG  
GGGGCCCCGGCTTTGAGGGATGCCACCGGTTCTGGACGCATGGCTGATTCCCTGAATGATGATGGTTCGCCGGGGG  
CTGCTTGCCTGGATTTCGCCGGGTGGTGGTTTGTGGTGGTCTCCTCTGCTGTGCTATCTCTGTCTGTACATGTTG  
GCCTGCACCCCAAAAGGTGACGAGGAGCAGCTGGCACTGCCAGGGCCAACAGCCCCACGGGGAAGGAGGGGTAC  
CAGGCCGTCTTCAGGAGTGGGAGGAGCAGCACCGCAACTACGTGAGCAGCCTGAAGCGGCAGATCGCAGAGCTC  
AAGGAGGAGCTGCAGGAGAGGAGTGAGCAGCTCAGGAATGGGCAGTACCAAGCCAGCGATGCTGCTGGCCTGGGT  
CTGGACAGGAGCCCCCAGAGAAAACCCAGGCCGACCTCCTGGCCTTCTGCACTCGCAGGTGGACAAGGCAGAG  
GTGAATGCTGGCGTCAAGCTGGCCACAGAGTATGCAAGCAGTGCCTTTTCGATAGCTTTACTCTACAGAAGGTGTAC  
CAGCTGGAGACTGGCCTTACCCGCCACCCCGAGGAGAAGCCTGTGAGGAAGGACAAGCGGGATGAGTTGGTGGAA  
GCCATTGAATCAGCCTTGAGACCCCTGAACAATCCTGCAGAGAACAGCCCCAATCACCCTCCTTACACGGCCTCT  
GATTTTCATAGAAGGGATCTACCGAACAGAAAGGGACAAAGGGACATTGTATGAGCTCACCTTCAAAGGGGACCAC  
AAACACGAATTCAAACGGCTCATCTTATTTTCGACCATTACGCCCCATCATGAAAGTGAAAAATGAAAAGCTCAAC  
ATGGCCAACACGCTTATCAATGTTATCGTGCCTCTAGCAAAAAGGGTGGACAAGTTCGGCAGTTTCATGCAGAAT  
TTCAGGGAGATGTGCATTGAGCAGGATGGGAGAGTCCATCTCACTGTTGTTTACTTTGGGAAAGAAGAAATAAAT  
GAAGTCAAAGGAATACTTGAAAACACTTCAAAGCTGCCAACTTCAGGAACCTTACCTTCATCCAGCTGAATGGA  
GAATTTTCTCGGGGAAAGGACTTGATGTTGGAGCCCGCTTCTGGAAGGGAAGCAACGTCCTTCTCTTTTCTGT  
GATGTGGACATCTACTTCACATCTGAATTCCTCAATACGTGTAGGCTGAATACACAGCCAGGGAAGAAGGTATTT  
TATCCAGTTCTTTTCAGTCAGTACAATCCTGGCATAATATACGGCCACCATGATGCAGTCCCTCCCTGGAAACAG  
CAGCTGGTCATAAAGAAGGAACTGGATTTTGGAGAGACTTTGGATTTGGGATGACGTGTGAGTATCGGTGAGAC  
TTCATCAATATAGGTGGGTTTGTCTGGACATCAAAGGCTGGGGCGGAGAGGATGTGCACCTTTATCGCAAGTAT  
CTCCACAGCAACCTCATAGTGGTACGGACGCCTGTGCGAGGACTCTTCCACCTCTGGCATGAGAAGCGCTGCATG  
GACGAGCTGACCCCCGAGCAGTACAAGATGTGCATGCACTCCAAGGCCATGAACGAGGCATCCCACGGCCAGCTG  
GGCATGCTGGTGTTCAGGCACAGATAGAGGCTCAGCCTTCGCAAAACAGAAACAGAAGACAAGTAGCAAAAAACA  
TGAACCTCCAGAGAAGGATTGTGGGAGACACTTTTTCTTTCTTTTGCAATTACTGAAAGTGGCTGCAACAGAGA  
AAAGACTTCCATAAAGGACGACAAAAGAATTGGACTGATGGGTGAGAGATGAGAAAGCCTCCGATTTCTCTGT  
TGGGCTTTTTTACAACAGAAATCAAATCTCCGCTTTGCCTGCAAAAGTAACCCAGTTGCACCTGTGAAGTGTCT  
GACAAAGGCAGAATGCTTGTGAGATTATAAGCCTAATGGTGTGGAGGTTTGTGATGCTTTACAATACACTGAGA  
CCTGTTGTTTTGTGTGCTCATTGAAATATTCATGATTTAAGAGCAGTTTGTGAAAAAATTCATTAGCATGAAAGG  
CAAGCATATTTCTCCTCATATGAATGAGCCTATCAGCAGGGCTCTAGTTTCTAGGAATGCTAAAATATCAGAAGG  
CAGGAGAGGAGATAGGCTTATTATGATACTAGTGAGTACATTAAGTAAAATAAAATGGACCAGAAAAGAAAAGAA  
ACCATAAATATCGTGTCTATTTTTCCCAAGATTAACCAAAAATAATCTGCTTATCTTTTGGTTGTCTTTTAA  
CTGTCTCCGTTTTTTTCTTTTATTTAAATGCACTTTTTTCCCTTGTGAGTTATAGTCTGCTTATTTAATTAC  
CACTTTGCAAGCCTTACAAGAGAGCACAAGTTGGCCTCACTTTTATATTTTTTAAGAAGATACTTTGAGATGCA  
TTATGAGAACTTTCAGTTCAAAGCATCAAATTGATGCCATATCCAAGGACATGCCAAATGCTGATTCTGTGAGGC  
ACTGAATGTGAGGCATTGAGACATAGGGAAGGAATGGTTTGTACTAATACAGACGTACAGATACTTTCTCTGAAG  
AGTATTTTCGAAGAGGAGCAACTGAACACTGGAGGAAAAGAAAATGACACTTTCTGCTTTACAGAAAAGGAACT  
CATTCAGACTGGTGATATCGTGATGACCTAAAAGTCAGAAACCACATTTTCTCCTCAGAAGTAGGGACCGCTTT  
CTTACCTGTTTAAATAAACCAAGTATACCGTGTGAACCAACAATCTTTTCAAACAGGGTGCTCCTCCTGG  
CTTCTGGCTTCCATAAGAAGAAATGGAGAAAAT  
CCAGAATCTAGTGGGATGGAAGTTTTTGTACATGTTATCCACCCAGGCCAGGTGGAAGTAACTGAATTTATTTT  
TTAAATTAAGCAGTTCTACTCAATACCAAGATGCTTCTGAAATTTGCAATTTTATTACCATTTCAAACATTTT  
TAAAAATAAATACAGTTAACATAGAGTGGTTTCTTCAATCATGTGAAAATTTATTAGCCAGCACCAGATGCATGAG  
CTAATTATCTCTTTGAGTCTTGTCTGTTTGTCTCACAGTAAACTCATGTTTAAAGCTTCAAGAACATTCAA  
GCTGTTGGTGTGTTAAAAAATGCATTGTATTGATTTGTGATTTGATGAAATTTAATTAACACAGGCCCA  
TGAATGGAAGGTGGTATTGCACAGCTAATAAATATGATTTGTGGATATGAA

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**FIGURE 72**

MMVRRGLLAWISRVVLLVLLCCAISVLYMLACTPKGDEEQLALPRANSPTGKEGYQAVLQE  
WEEQHRNYVSSLKRQIAQLKEELQERSEQLRNGQYQASDAAGLGLDRSPPEKTQADLLAFLHS  
QVDKAEVNAGVKLATEYAAVPFDSFTLQKVYQLETGLTRHPEEKPV RKDKRDELVEAIESALE  
TLNNPAENSPNHRPYTASDFIEGIYRTERDKGTLYELTFKGDHKHEFKRLILFRPFSPIMKVK  
NEKLNMAANTLINVIVPLAKRVDKFRQFMQNFREMCIEQDGRVHLTVVYFGKEEINEVKGILEN  
TSKAANFRNFTFIQLNGEFSRGKGLDVGARFWKGSNVLLFFCDVDIYFTSEFLNTCRLNTQPG  
KKVFYFVLF SQYNPGI IYGHHD AVPPLEQQLV IKKETGFWRDFGFGMTCQYRSDFINIGGFDL  
DIKGWGGEDVHLYRKYLHSNLIVVRTPV RGLFHLWHEKRCMDELTP EQYKMCMQSKAMNEASH  
GQLGMLVFRHEIEAHLRKQKQKTSSKKT

**Important features:****Signal peptide:**

amino acids 1-27

**N-glycosylation sites.**

amino acids 315-319, 324-328

**N-myristoylation sites.**

amino acids 96-102, 136-142, 212-218, 311-317, 339-345, 393-399

**Amidation site.**

amino acids 377-381

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**FIGURE 73**

GAGACTGCAGAGGGAGATAAAGAGAGAGGGCAAAGAGGCAGCAAGAGATTTGTCCTGGGGATC  
CAGAAACCCATGATACCCTACTGAACACCGAATCCCCTGGAAGCCCACAGAGACAGAGACAGC  
AAGAGAAGCAGAGATAAATACTACCTCAGCCAGGAGCTCGCTCGCTCTCTCTCTCTCTCTCA  
CTCCTCCCTCCCTCTCTCTCTGCCTGTCTAGTCCTCTAGTCCTCAAATTCCCAGTCCCCTGC  
ACCCCTTCTCTGGGACACTATGTTGTTCTCCGCCCTCCTGCTGGAGGTGATTTGGATCCTGGCT  
GCAGATGGGGGTCAACACTGGACGTATGAGGGCCCACATGGTCAGGACCATTGGCCAGCCTCT  
TACCCTGAGTGTGGAAACAATGCCAGTCGCCCATCGATATTCAGACAGACAGTGTGACATTT  
GACCCTGATTTGCCTGCTCTGCAGCCCCACGGATATGACCAGCCTGGCACCGAGCCTTTGGAC  
CTGCACAACAATGGCCACACAGTGCAACTCTCTCTGCCCTCTACCCTGTATCTGGGTGGACTT  
CCCCGAAAATATGTAGCTGCCAGCTCCACCTGCACTGGGGTCAGAAAGGATCCCAGGGGGG  
TCAGAACACCAGATCAACAGTGAAGCCACATTTGCAGAGCTCCACATTGTACATTATGACTCT  
GATTCCTATGACAGCTTGAGTGAGGCTGCTGAGAGGCCCTCAGGGCCTGGCTGTCCTGGGCATC  
CTAATTGAGGTGGGTGAGACTAAGAATATAGCTTATGAACACATTCTGAGTCACTTGCATGAA  
GTCAGGCATAAAGATCAGAAGACCTCAGTGCCTCCCTTCAACCTAAGAGAGCTGCTCCCCAAA  
CAGCTGGGGCAGTACTTCCGCTACAATGGCTCGCTCACAACTCCCCCTTGCTACCAGAGTGTG  
CTCTGGACAGTTTTTTTATAGAAGGTCCCAGATTTCAATGGAACAGCTGGAAAAGCTTCAGGGG  
ACATTGTTCTCCACAGAAGAGGAGCCCTCTAAGCTTCTGGTACAGAACTACCGAGCCCTTCAG  
CCTCTCAATCAGCGCATGGTCTTTGCTTCTTTCATCCAAGCAGGATCCTCGTATACCACAGGT  
GAAATGCTGAGTCTAGGTGTAGGAATCTTGTTGGCTGTCTCTGCCTTCTCCTGGCTGTTTAT  
TTCATTGCTAGAAAGATTCGGAAGAAGAGGCTGGAAAACCGAAAGAGTGTGGTCTTCACCTCA  
GCACAAGCCACGACTGAGGCATTAAATTCCCTTCTCAGATACCATGGATGTGGATGACTTCCCTT  
CATGCCTATCAGGAAGCCTCTAAATGGGGTGTAGGATCTGGCCAGAAACACTGTAGGAGTAG  
TAAGCAGATGTCCTCCTTCCCCTGGACATCTCTTAGAGAGGAATGGACCCAGGCTGTCATTCC  
AGGAAGAAGCTGCAGAGCCTTCAGCCTCTCCAAACATGTAGGAGGAATGAGGAAATCGCTGTG  
TTGTTAATGCAGAGANCAAACCTCTGTTTAGTTGCAGGGGAAGTTTGGGATATACCCCAAAGTC  
CTCTACCCCTCACTTTTATGGCCCTTTCCTAGATATACTGCGGGATCTCTCCTTAGGATAA  
AGAGTTGCTGTTGAAGTTGTATATTTTTGATCAATATATTTGGAAATTAAAGTTTCTGACTTT

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**FIGURE 74**

MLFSALLLEVIWILAADGGQHWTYEGPHGQDHPASYPECGNNAQSPIDIQTDSVTFDPDLPA  
LQPHGYDQPGTEPLDLHNNGHTVQLSLPSTLYLGGLPRKYVAAQLHLHWGQKGSPGGSEHQIN  
SEATFAELHIVHYDSDSYDSLSEAAERPQGLAVLGILIEVGETKNIAYEHILSHLHEVRHKDQ  
KTSVPPFNLRELLPKQLGQYFRYNGSLTTPPCYQSVLWTVFYRRSQISMEQLEKLQGTLFSTE  
EEPSKLLVQNYRALQPLNQRMVFASFIQAGSSYTTGEMLSLGVGILVGCLCLLLAVYFIARKI  
RKKRLENRKSUVFTSAQATTEA

**Important features of the protein:****Signal peptide:**

amino acids 1-15

**Transmembrane domain:**

amino acids 291-310

**N-glycosylation site.**

amino acids 213-216

**Eukaryotic-type carbonic anhydrases proteins**

amino acids 197-245, 104-140, 22-69

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**FIGURE 75**

TGCCGCTGCCGCCGCTGCTGCTGTTGCTCCTGGCGGCGCCTTGGGGACGGGCAGTTCCCTGTG  
TCTCTGGTGGTTTGCCTAAACCTGCAAACATCACCTTCTTATCCATCAACATGAAGAATGTCC  
TACAATGGACTCCACCAGAGGGTCTTCAAGGAGTTAAAGTTACTTACACTGTGCAGTATTTCA  
TCACAAATTGGCCCACCAGAGGTGGCACTGACTACAGATGAGAAGTCCATTTCTGTTGTCCTG  
ACAGCTCCAGAGAAGTGGAAGAGAAATCCAGAAGACCTTCTGTTTCCATGCAACAAATATAC  
TCCAATCTGAAGTATAACGTGTCTGTGTTGAATACTAAATCAAACAGAACGTGGTCCCAGTGT  
GTGACCAACCACACGCTGGTGCTCACCTGGCTGGAGCCGAACACTCTTTACTGCGTACACGTG  
GAGTCCTTCGTCCCAGGGCCCCCTCGCCGTGCTCAGCCTTCTGAGAAGCAGTGTGCCAGGACT  
TTGAAAGATCAATCATCAGAGTTCAAGGCTAAAATCATCTTCTGGTATGTTTTGCCCATATCT  
ATTACCGTGTTTCTTTTTTCTGTGATGGGCTATTCCATCTACCGATATATCCACGTTGGCAAA  
GAGAAACACCCAGCAAATTTGATTTTGATTTATGGAAATGAATTTGACAAAAGATTCTTTGTG  
CCTGCTGAAAAAATCGTGATTAACTTTATCACCCCTCAATATCTCGGATGATTCTAAATTTCT  
CATCAGGATATGAGTTTACTGGGAAAAAGCAGTGATGTATCCAGCCTTAATGATCCTCAGCCC  
AGCGGGAACCTGAGGCCCCCTCAGGAGGAAGAGGAGGTGAAACATTTAGGGTATGCTTCGCAT  
TTGATGGAAATTTTTTGTGACTCTGAAGAAAACACGGAAGGTACTTCTCTCACCCAGCAAGAG  
TCCCTCAGCAGAACAATACCCCCGGATAAAACAGTCATTGAATATGAATATGATGTGAGAACC  
ACTGACATTTGTGCGGGGCTGAAGAGCAGGAGCTCAGTTTGCAGGAGGAGGTGTCCACACAA  
GGAACATTATTGGAGTCGCAGGCAGCGTTGGCAGTCTTGGGCCCCGAAACGTTACAGTACTCA  
TACACCCCTCAGCTCCAAGACTTAGACCCCTGGCGCAGGAGCACACAGACTCGGAGGAGGGG  
CCGGAGGAAGAGCCATCGACGACCCTGGTCGACTGGGATCCCCAACTGGCAGGCTGTGTATT  
CCTTCGCTGTCCAGCTTCGACCAGGATTGAGAGGGCTGCGAGCCTTCTGAGGGGGATGGGCTC  
GGAGAGGAGGGTCTTCTATCTAGACTCTATGAGGAGCCGGCTCCAGACAGGCCACCAGGAGAA  
AATGAAACCTATCTCATGCAATTCATGGAGGAATGGGGGTATATGTGCAGATGGAAAACTGA  
TGCCAACACTTCCTTTTGCCTTTTGTTCCTGTGCAAACAAGTGAGTCACCCCTTTGATCCCA  
GCCATAAAGTACCTGGGATGAAAGAAGTTTTTTCAGTTTGTGAGTGTCTGTGAGAATTACTT  
ATTTCTTTTCTCTATTCTCATAGCACGTGTGTGATTGGTTCATGCATGTAGGTCTCTTAACAA  
TGATGGTGGGCTCTGGAGTCCAGGGGCTGGCCGTTGTTCTATGCAGAGAAAGCAGTCAATA  
AATGTTTGCCAGACTGGGTGCAGAATTTATTCAGGTGGGTGT

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**FIGURE 76**

MSYNGLHQRVFKELKLLTLCSSIQIGPPEVALTTDEKSISVVLTAPEKWKRNPEDLPVSMQQ  
IYSNLKYNVSVLNTKSNRTWSQCVTNHTLVLTWLEPNTLYCVHVESFVPGPPRAQPSEKQCA  
RTLKDQSSEFKAKIIFWYVLPISITVFLFSVMGYSIYRYIHVGKEKHPANLILYIGNEFDKRF  
FVPAEKIVINFITLNISSDDSKISHQDMSLLGKSSDVSSLNDPQPSGNLRPPQEEEEVKHLGYA  
SHLMEIFCDSEENTEGETSLTQQESLSRTIPDPKTVIEYEYDVRTTDICAGPEEQELSLQEEVS  
TQGTLLSQAAALAVLGPQTLQYSYTPQLQDLPLAQEHTDSEEGPEEEPSTTLVDWDPQTGRL  
CIPSLSSFDQDSEGCEPSEGDLGEEGLLSRLYEPPAPDRPPGENETYLMQFMEEWGLYVQMEN

**Important features:****Signal peptide:**

amino acids 1-28

**Transmembrane domain:**

amino acids 140-163

**N-glycosylation sites.**

amino acids 71-74, 80-83, 89-92, 204-207, 423-426

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**FIGURE 77**

GAGGAGCGGGCCGAGGACTCCAGCGTGCCAGGTCTGGCATCCTGCACTTGCTGCCCTCTGAC  
ACCTGGGAAGATGGCCGGCCCGTGGACCTTCACCCTTCTCTGTGGTTTGCTGGCAGCCACCTT  
GATCCAAGCCACCCTCAGTCCCACTGCAGTTCTCATCCTCGGCCCAAAGTCATCAAAGAAAA  
GCTGACACAGGAGCTGAAGGACCACAACGCCACCAGCATCCTGCAGCAGCTGCCGCTGCTCAG  
TGCCATGCGGGAAAAGCCAGCCGGAGGCATCCCTGTGCTGGGCAGCCTGGTGAACACCGTCTT  
GAAGCACATCATCTGGCTGAAGGTCATCACAGCTAACATCCTCCAGCTGCAGGTGAAGCCCTC  
GGCCAATGACCAGGAGCTGCTAGTCAAGATCCCCCTGGACATGGTGGCTGGATTCAACACGCC  
CCTGGTCAAGACCATCGTGGAGTTCCACATGACGACTGAGGCCCAAGCCACCATCCGCATGGA  
CACCAGTGCAAGTGGCCCCACCCGCCTGGTCCTCAGTGACTGTGCCACCAGCCATGGGAGCCT  
GCGCATCCAAGTCTGTATAAGCTCTCCTTCCTGGTGAACGCCTTAGCTAAGCAGGTCATGAA  
CCTCCTAGTGCCATCCCTGCCCAATCTAGTGAAAAACCAGCTGTGTCCCGTGATCGAGGCTTC  
CTTCAATGGCATGTATGCAGACCTCCTGCAGCTGGTGAAGGTGCCCATTTCCCTCAGCATTGA  
CCGTCTGGAGTTTGACCTTCTGTATCCTGCCATCAAGGGTGACACCATTACAGCTCTACCTGGG  
GGCCAAGTTGTTGGAATCACAGGGAAAGGTGACCAAGTGGTTCAATAACTCTGCAGCTTCCCT  
GACAATGCCACCCTGGACAACATCCCGTTTCCAGCCTCATCGTGAGTCAGGACGTGGTGAAAGC  
TGCAGTGGCTGCTGTGCTCTCTCCAGAAGAATTCATGGTCCTGTTGGACTCTGTGCTTCTCTGA  
GAGTGCCCATCGGCTGAAGTCAAGCATCGGGCTGATCAATGAAAAGGCTGCAGATAAGCTGGG  
ATCTACCCAGATCGTGAAGATCCTAACTCAGGACACTCCCGAGTTTTTTATAGACCAAGGCCA  
TGCCAAGGTGGCCCAACTGATCGTGCTGGAAGTGTTTCCCTCCAGTGAAGCCCTCCGCCCTTT  
GTTACCCTGGGCATCGAAGCCAGCTCGGAAGCTCAGTTTTTACACCAAAGGTGACCAACTTAT  
ACTCAACTTGAATAACATCAGCTCTGATCGGATCCAGCTGATGAACTCTGGGATTGGCTGGTT  
CCAACCTGATGTTCTGAAAAACATCATCACTGAGATCATCCACTCCATCCTGCTGCCGAACCA  
GAATGGCAAATTAAGATCTGGGGTCCCAGTGTCATTGGTGAAGGCCTTGGGATTCGAGGCAGC  
TGAGTCCTCACTGACCAAGGATGCCCTTGTGCTTACTCCAGCCTCCTTGTGGAAACCCAGCTC  
TCCTGTCTCCAGTGAAGACTTGATGGCAGCCATCAGGGAAGGCTGGGTCCCAGCTGGGAGT  
ATGGGTGTGAGCTCTATAGACCATCCCTCTCTGCAATCAATAAACACTTGCCTGTGAAAAA

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**FIGURE 78**

MAGPWTFTLLCGLLAATLIQATLSPTAVLILGPKVIKEKLTQELKDHNATSILQQPLLSAMR  
EKPAGGIPVLGSLVNTVLKHIIWLKVITANILQLQVKPSANDQELLVKIPLDMVAGFNTPLVK  
TIVEFHMTTEAQATIRMDTSASGPTRLVLSDCATSHGSLRIQLLYKLSFLVNALAKQVMNLLV  
PSLPNLVKNQLCPVIEASFNGMYADLLQLVKVPISLSIDRLEFDLLYPAIKGDTIQLYLGAKL  
LDSQGKVTKWFNNSAASLTMPTLDNIPFSLIVSQDVVKAAVAVALSPEEFMVLLDSVLPESAH  
RLKSSIGLINEKAADKLGSTQIVKILTQDTPEFFIDQGHAKVAQLIVLEVFPSSSEALRPLFTL  
GIEASSEAQFYTKGDQLILNLNNISSDRIQLMNSGIGWFQPDVLKNIITEIIHSILLPNQNGK  
LRSGVPVSLVKALGFEEAESSLTkdALVLTpasLWKpSSpVSQ

**Important features of the protein:**

**Signal peptide:**

amino acids 1-21

**N-glycosylation sites.**

amino acids 48-51, 264-267, 401-404

**Glycosaminoglycan attachment site.**

amino acids 412-415

**LBP / BPI / CETP family proteins.**

amino acids 407-457



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**FIGURE 79**

GAGAGAAGTCAGCCTGGCAGAGAGACTCTGAAATGAGGGATTAGAGGTGTTCAAGGAGCAAGA  
GCTTCAGCCTGAAGACAAGGGAGCAGTCCCTGAAGACGCTTCTACTGAGAGGTCTGCCATGGC  
CTCTCTTGGCCTCCAACCTTGTGGGCTACATCCTAGGCCTTCTGGGGCTTTTGGGCACACTGGT  
TGCCATGCTGCTCCCCAGCTGGAAAAACAAGTTCTTATGTCGGTGCCAGCATTGTGACAGCAGT  
TGGCTTCTCCAAGGGCCTCTGGATGGAATGTGCCACACACAGCACAGGCATCACCCAGTGTGA  
CATCTATAGCACCCCTTCTGGGCCTGCCCCGCTGACATCCAGGCTGCCCAGGCCATGATGGTGAC  
ATCCAGTGCAATCTCCTCCCTGGCCTGCATTATCTCTGTGGTGGGCATGAGATGCACAGTCTT  
CTGCCAGGAATCCCGAGCCAAAGACAGAGTGGCGGTAGCAGGTGGAGTCTTTTTTCATCCTTGG  
AGGCCTCCTGGGATTCAATTCCTGTTGCCTGGAATCTTCATGGGATCCTACGGGACTTCTACTC  
ACCACTGGTGCCTGACAGCATGAAATTTGAGATTGGAGAGGCTCTTTACTTGGGCATTATTTCT  
TTCCCTGTTCTCCCTGATAGCTGGAATCATCCTCTGCTTTTCCCTGCTCATCCCAGAGAAATCG  
CTCCAACCTACTACGATGCCTACCAAGCCCAACCTCTTGCCACAAGGAGCTCTCCAAGGCCTGG  
TCAACCTCCCAAAGTCAAGAGTGAGTTCAATTCCCTACAGCCTGACAGGGTATGTGTGAAGAAC  
CAGGGGCCAGAGCTGGGGGGTGGCTGGGTCTGTGAAAAACAGTGGACAGCACCCCGAGGGCCA  
CAGGTGAGGGACACTACCACTGGATCGTGTGAGAAGGTGCTGCTGAGGATAGACTGACTTTGG  
CCATTGGATTGAGCAAAGGCAGAAATGGGGGCTAGTGTAACAGCATGCAGGTGGAATTGCCAA  
GGATGCTCGCCATGCCAGCCTTTCTGTTTTCTCACCTTGCTGCTCCCCTGCCCTAAGTCCCC  
AACCCTCAACTTGAAACCCCATTCCTTAAGCCAGGACTCAGAGGATCCCTTTGCCCTCTGGT  
TTACCTGGGACTCCATCCCCAAACCCACTAATCACATCCCACTGACTGACCCTCTGTGATCAA  
AGACCCTCTCTCTGGCTGAGGTGGCTCTTAGCTCATTGCTGGGGATGGGAAGGAGAAGCAGT  
GGCTTTTGTGGGCATTGCTCTAACCTACTTCTCAAGCTTCCCTCCAAAGAACTGATTGGCCC  
TGGAACCTCCATCCCACTCTTGTTATGACTCCACAGTGTCCAGACTAATTTGTGCATGAACTG  
AAATAAAACCATCCTACGGTATCCAGGGAACAGAAAGCAGGATGCAGGATGGGAGGACAGGAA  
GGCAGCCTGGGACATTTAAAAAATA

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**FIGURE 80**

MASLGLQLVG YILGLLGLLGTLVAMLLPSWKTSSYVGASIVTAVGFSKGLWMECATHSTGITQ  
CDIYSTLLGLPADIQAAQAMMVTSSAIISSLACIISVVGMRCTVFCQESRAKDRVAVAGGVFFI  
LGLLGFIPVAWNLHGILRDFYSPLVPDSMKFEIGEALYLGIISSLFSLIAGIILCFSCSSQR  
NRSNYYDAYQAQPLATRSSPRPGQPPKVKSEFNSYSLTGYV

**Important features of the protein:****Signal peptide:**

amino acids 1-24

**Transmembrane domains:**

amino acids 82-102, 117-140, 163-182

**N-glycosylation site.**

amino acids 190-193

**PMP-22 / EMP / MP20 family proteins.**

amino acids 46-59

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**FIGURE 81**

CCCACGCGTCCGCGCCTCTCCCTTCTGCTGGACCTTCCTTCGTCTCTCCATCTCTCCCTCCTT  
TCCCCGCGTTCTCTTTCCACCTTTCTCTTCTTCCACCTTAGACCTCCCTTCCTGCCCTCCTT  
TCCTGCCACCGCTGCTTCCTGGCCCTTCTCCGACCCCGCTCTAGCAGCAGACCTCCTGGGGT  
CTGTGGGTTGATCTGTGGCCCCCTGTGCCTCCGTGTCTTTTCGTCTCCCTTCCTCCCGACTCC  
GCTCCCGGACCAGCGGCCCTGACCCTGGGGAAAGG**ATG**GTTCCTCGAGGTGAGGGTCTCTCCTC  
CTTGCTGGGACTCGCGCTGCTCTGGTTCCTTGGACTCCCACGCTCGAGCCCGCCAGACAT  
GTTCTGCCTTTTCCATGGGAAGAGATACTCCCCGGCGAGAGCTGGCACCCCTACTTGGAGCC  
ACAAGGCCTGATGTACTGCCTGCGCTGTACCTGCTCAGAGGGCGCCCATGTGAGTTGTTACCG  
CCTCCACTGTCCGCCTGTCCACTGCCCCAGCCTGTGACGGAGCCACAGCAATGCTGTCCCAA  
GTGTGTGGAACCTCACACTCCCTCTGGACTCCGGGCCCCACCAAAGTCCTGCCAGCACAAACGG  
GACCATGTACCAACACGGAGAGATCTTCAGTGCCCATGAGCTGTTCCTTCCCGCTGCCCAA  
CCAGTGTGTCTCTGCAGCTGCACAGAGGGCCAGATCTACTGCGGCCCTCACAACCTGCCCCGA  
ACCAGGCTGCCCAGCACCCCTCCCACTGCCAGACTCCTGCTGCCAAGCCTGCAAAGATGAGGC  
AAGTGAGCAATCGGATGAAGAGGACAGTGTGCAGTCGCTCCATGGGGTGAGACATCCTCAGGA  
TCCATGTTCCAGTGATGCTGGGAGAAAGAGAGGCCCGGGCACCCAGCCCCACTGGCCTCAG  
CGCCCCCTCTGAGCTTCATCCCTCGCCACTTCAGACCCAAGGGAGCAGGCAGCACAACTGTCAA  
GATCGTCCTGAAGGAGAAACATAAGAAAGCCTGTGTGCATGGCGGGAAGACGTACTCCCACGG  
GGAGGTGTGGCACCCGGCCTTCCGTGCCTTCGGCCCCCTTGCCCTGCATCCTATGCACCTGTGA  
GGATGGCCGCCAGGACTGCCAGCGTGTGACCTGTCCCACCGAGTACCCCTGCCGTACCCCCGA  
GAAAGTGGCTGGGAAGTGCTGCAAGATTTGCCCAGAGGACAAAGCAGACCCTGGCCACAGTGA  
GATCAGTTCTACCAGGTGTCCCAAGGCACCGGGCCGGGTCTCGTCCACACATCGGTATCCCC  
AAGCCCAGACAACCTGCGTCGCTTTGCCCTGGAACACGAGGCCTCGGACTTGGTGAGATCTA  
CCTCTGGAAGCTGGTAAAAGATGAGGAACTGAGGCTCAGAGAGGTGAAGTACCTGGCCCAAG  
GCCACACAGCCAGAATCTTCCACTTGACTCAGATCAAGAAAGTCAGGAAGCAAGACTTCCAGA  
AAGAGGCACAGCACTTCCGACTGCTCGCTGGCCCCCACGAAGGTCAGTGAACGTCTTCCTAG  
CCCAGACCCTGGAGCTGAAGGTCACGGCCAGTCCAGACAAAGTGACCAAGACATAACAAAGAC  
**CTAA**CAGTTGCAGATATGAGCTGTATAATTGTTGTTATTATATATTAATAAATAAGAAGTTGC  
ATTACCCTCAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 82**

MVPEVRVLSSLLGLALLWFPLDSHARARPD MFCLFHGKRYSPGESWHPYLEPQGLMYCLRCTC  
SEGAHVSCYRLHCPPVHCPQPVTEPQQCCPKCEPHTPSGLRAPPKSCQHNGTMYQHGEIFSA  
HELFPSRLPNQCVLCSTEGQIYCGLTTCPEPGCPAPLPLPDSCCQACKDEASEQSDEEDSVQ  
SLHGVRHPQDPCSSDAGRKRGPPTAPTGLSAPLSFI PRHFRPKGAGSTTVKIVLKEKHKKAC  
VHGGKTYSHGEVWHPAFRAFGPLPCILCTCEDGRQDCQRVTCPT EYPCRHPK VAGKCKKICP  
EDKADPGHSEISSTRCPKAPGRVLVHTSVSPSPDNLRRFALEHEASDLVEIYLWKLVKDEETE  
AQRGEVPGPRPHSQNLPLDSDQESQEARLPERGTALPTARWPPRRSLERLPSPDPGAEGHGQS  
RQSDQDITKT

**Signal peptide:**

amino acids 1-25

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**FIGURE 83**

GACAGCTGTGTCTCGATGGAGTAGACTCTCAGAACAGCGCAGTTTGCCCTCCGCTCACGCAGA  
GCCTCTCCGTGGCTTCCGCACCTTGAGCATTAGGCCAGTTCTCCTCTTCTCTCTAATCCATCC  
GTCACCTCTCCTGTCAATCCGTTTCCATGCCGTGAGGTCCATTACAGAACACATCCATGGCTC  
TCATGCTCAGTTTGGTTCTGAGTCTCCTCAAGCTGGGATCAGGGCAGTGGCAGGTGTTTGGGC  
CAGACAAGCCTGTCCAGGCCCTTGGTGGGGGAGGACGCAGCATTCTCCTGTTTCCTGTCTCCTA  
AGACCAATGCAGAGGCCATGGAAGTGCGGTTCTTCAGGGGCCAGTTCTCTAGCGTGGTCCACC  
TCTACAGGGACGGGAAGGACCAGCCATTTATGCAGATGCCACAGTATCAAGGCAGGACAAAAC  
TGGTGAAGGATTCTATTGCGGAGGGGCGCATCTCTCTGAGGCTGGAAAACATTACTGTGTTGG  
ATGCTGGCCTCTATGGGTGCAGGATTAGTTCCCAGTCTTACTACCAGAAGGCCATCTGGGAGC  
TACAGGTGTCAGCACTGGGCTCAGTTCTCTCATTTCCATCACGGGATATGTTGATAGAGACA  
TCCAGCTACTCTGTCAGTCTCTCGGGCTGGTTCCCCCGGCCACAGCGAAGTGGAAAGGTCCAC  
AAGGACAGGATTTGTCCACAGACTCCAGGACAAACAGAGACATGCATGGCCTGTTTGATGTGG  
AGATCTCTCTGACCGTCCAAGAGAACGCCGGGAGCATATCCTGTTCCATGCGGCATGCTCATC  
TGAGCCGAGAGGTGGAATCCAGGGTACAGATAGGAGATACCTTTTTTCGAGCCTATATCGTGGC  
ACCTGGCTACCAAAGTACTGGGAATACTCTGCTGTGGCCTATTTTTTGGCATTGTTGGACTGA  
AGATTTTCTTCTCAAATTCAGTGGAAAATCCAGGCGGAACTGGACTGGAGAAGAAAGCACG  
GACAGGCAGAATTGAGAGACGCCCCGAAACACGCAGTGGAGGTGACTCTGGATCCAGAGACGG  
CTCACCCGAAGCTCTGCGTTTCTGATCTGAAAATGTAACCCATAGAAAAGCTCCCCAGGAGG  
TGCCTCACTCTGAGAAGAGATTTACAAGGAAGAGTGTGGTGGCTTCTCAGAGTTTCCAAGCAG  
GGAAACATTACTGGGAGGTGGACGGAGGACACAATAAAAGGTGGCGCGTGGGAGTGTGCCGGG  
ATGATGTGGACAGGAGGAAGGAGTACGTGACTTTGTCTCCCGATCATGGGTACTGGGTCTCTCA  
GACTGAATGGAGAACATTTGTATTTACATTAAATCCCCGTTTTATCAGCGTCTTCCCCAGGA  
CCCCACCTACAAAATAGGGGTCTTCTGGAATATGAGTGTGGGACCATCTCCTTCTTCAACA  
TAAATGACCAGTCCCTTATTTATACCCTGACATGTGCGTTTGAAGGCTTATTGAGGCCCTACA  
TTGAGTATCCGTCTATAATGAGCAAAATGGAATCCCATAGTCATCTGCCCAGTCACCCAGG  
AATCAGAGAAAGAGGCCTCTTGGCAAAGGGCCTCTGCAATCCCAGAGACAAGCAACAGTGAGT  
CCTCCTCACAGGCAACCACGCCCTTCTCCCCAGGGGTGAAATGTAGGATGAATCACATCCCA  
CATTCTTCTTTAGGGATATTAAGGTCTCTCTCCCAGATCCAAAGTCCCGCAGCAGCCGGCCAA  
GGTGGCTTCCAGATGAAGGGGGACTGGCCTGTCCACATGGGAGTCAGGTGTCATGGCTGCCCT  
GAGCTGGGAGGGAAGAAGGCTGACATTACATTTAGTTTGCTCTCACTCCATCTGGCTAAGTGA  
TCTTGAAATACCACCTCTCAGGTGAAGAACCGTCAGGAATCCCATCTCACAGGCTGTGGTGT  
AGATTAAGTAGACAAGGAATGTGAATAATGCTTAGATCTTATTGATGACAGAGTGTATCCTAA  
TGGTTTGTTTCATTATATTACACTTTCAGTAAAAAA

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**FIGURE 84**

MALMLSLVLSLLKLGSGQWQVEGPDKPVQALVGEDAAFSCFLSPKTNAEAMEVRFFRGQFSSV  
VHLYRDGKDQPFMQMPQYQGR TKLVKDSIAEGRISLRLENITVLDAGLYGCRIS SQSYQKAI  
WELQVSALGSVPLISITGYVDRDIQLLCQSSGWFPRTAKWKGPQGQDLSTDSRTNRDMHGLF  
DVEISLTVQENAGSISCSMRHAHLSREVESRVQIGDTFFEPISWHLATKVLGILCCGLFFGIV  
GLKIFFSKFQWKIQAE LDWRRKHGQAE LRDARKHAVEVT LDPETAHPKLCVSDLKTVTHR KAP  
QEVPHSEKRFRTRKSVVASQSFQAGKH YWEVDGGHNKRWRVGVC RDDVD RRKEYVTLS PDHGYW  
VLR LN GEHL YFTLNPRFISVFPRT PPTKIGVFLDYECGTISFFNINDQSLIYTLTCRFEGLLR  
PYIEYPSYNEQNGTPIVICPVTQESEKEASWQRASAI PETSNSSESSQATTPFLPRGEM

**Signal peptide:**

amino acids 1-17

**Transmembrane domain:**

amino acids 239-255

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**FIGURE 85**

AACAGACGTTCCCTCGCGGCCCTGGCACCTCTAACCCCAGACATGCTGCTGCTGCTGCTGCCC  
CTGCTCTGGGGGAGGGAGAGGGCGGAAGGACAGACAAGTAAACTGCTGACGATGCAGAGTTCC  
GTGACGGTGACAGGAAGGCCTGTGTGTCCATGTGCCCTGCTCCTTCTCCTACCCCTCGCATGGC  
TGGATTTACCCTGGCCCAGTAGTTTCATGGCTACTGGTTCCGGGAAGGGGCCAATACAGACCAG  
GATGCTCCAGTGGCCACAAACAACCCAGCTCGGGCAGTGTGGGAGGAGACTCGGGACCGATT  
CACCTCCTTGGGGACCCACATACCAAGAATTGCACCCTGAGCATCAGAGATGCCAGAAGAAGT  
GATGCGGGGAGATACTTCTTTTCGTATGGAGAAAGGAAGTATAAAATGGAATTATAAACATCAC  
CGGCTCTCTGTGAATGTGACAGCCTTGACCCACAGGCCCAACATCCTCATCCCAGGCACCCTG  
GAGTCCGGCTGCCCCCAGAATCTGACCTGCTCTGTGCCCTGGGCCTGTGAGCAGGGGACACCC  
CCTATGATCTCCTGGATAGGGACCTCCGTGTCCCCCTGGACCCCTCCACCACCCGCTCCTCG  
GTGCTCACCCCTCATCCACAGCCCCAGGACCATGGCACCAGCCTCACCTGTCAGGTGACCTTC  
CCTGGGGCCAGCGTGACCACGAACAAGACCGTCCATCTCAACGTGTCCTACCCGCCTCAGAAC  
TTGACCATGACTGTCTTCCAAGGAGACGGCACAGTATCCACAGTCTTGGGAAATGGCTCATCT  
CTGTCACTCCCAGAGGGCCAGTCTCTGCGCCTGGTCTGTGCAGTTGATGCAGTTGACAGCAAT  
CCCCCTGCCAGGCTGAGCCTGAGCTGGAGAGGCCTGACCCTGTGCCCCTCACAGCCCTCAAAC  
CCGGGGGTGCTGGAGCTGCCTTGGGTGCACCTGAGGGATGCAGCTGAATTCACCTGCAGAGCT  
CAGAACCCTCTCGGCTCTCAGCAGGTCTACCTGAACGTCTCCCTGCAGAGCAAAGCCACATCA  
GGAGTGACTCAGGGGGTGGTCGGGGGAGCTGGAGCCACAGCCCTGGTCTTCCTGTCCTTCTGC  
GTCATCTTCGTTGTAGTGAGGTCCTGCAGGAAGAAATCGGCAAGGCCAGCAGCGGGCGTGGGA  
GATACGGGCATAGAGGATGCAAACGCTGTGAGGGGTTTACGCTCTCAGGGGGCCCCTGACTGAA  
CCTTGGGCAGAAGACAGTCCCCCAGACCAGCCTCCCCCAGCTTCTGCCCCTCCTCAGTGGGG  
GAAGGAGAGCTCCAGTATGCATCCCTCAGCTTCCAGATGGTGAAGCCTTGGGACTCGCGGGGA  
CAGGAGGCCACTGACACCGAGTACTCGGAGATCAAGATCCACAGATGAGAAACTGCAGAGACT  
CACCCTGATTGAGGGATCACAGCCCCTCCAGGCAAGGGAGAAGTCAGAGGCTGATTCTTGTAG  
AATTAACAGCCCTCAACGTGATGAGCTATGATAACACTATGAATTATGTGCAGAGTGAAAAGC  
ACACAGGCTTTAGAGTCAAAGTATCTCAAACCTGAATCCACACTGTGCCCTCCCTTTTATTTT  
TTTAACTAAAAGACAGACAAATTCCTA

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**FIGURE 86**

MLLLLLPLLWGRERAEGQTSKLLTMQSSVTVQEGLCVHVPCSFSPSHGWIYPGPVVHGYWFR  
EGANTDQDAPVATNNPARAVWEETRDREHLLGDPHTKNCTLSIRDARRSDAGRYFFRMEKGS  
KWNKHHRLSVNVTALTHRPNILIPGTLESGCPQNLTCVWPWACEQGTPPMISWIGTSVSPLD  
PSTTRSSVLTLLIPQPQDHGTS LTCQVTFFPGASVTTNKTVHLNVSYPPQNLMTVFQGDGTVST  
VLGNGSSLSPGQSLRLVCAVDAVDSNPPARLSLSWRGLTLCPSQPSNPGVLELPWVHLRDA  
AEFTCRAQNPLGSQQVYLNVSLSKATSGVTQGVVGGAGATALVFLSFCVIFVVVRSCRKSA  
RPAAGVGDGTGIEDANAVRGSASQGPLEPWAEDSPPDQPPASARSSVGEGLQYASLSFQMV  
KPWDSRGQEATDTEYSEIKIHR

**Signal peptide:**

amino acids 1-15

**Transmembrane domain:**

amino acids 351-370



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**FIGURE 87**

AGAAAGCTGCACTCTGTTGAGCTCCAGGGCGCAGTGGAGGGAGGGAGTGAAGGAGCTCTCTGT  
ACCCAAGGAAAAGTGCAGCTGAGACTCAGACAAGATTACAATGAACCAACTCAGCTTCCTGCTG  
TTTCTCATAGCGACCACCAGAGGATGGAGTACAGATGAGGCTAATACTTACTTCAAGGAATGG  
ACCTGTTCTTCGTCTCCATCTCTGCCCAGAAGCTGCAAGGAAATCAAAGACGAATGTCCTAGT  
GCATTTGATGGCCTGTATTTTCTCCGCACTGAGAATGGTGTATCTACCAGACCTTCTGTGAC  
ATGACCTCTGGGGGTGGCGGCTGGACCCTGGTGGCCAGCGTGCATGAGAATGACATGCGTGGG  
AAGTGCACGGTGGGCGATCGCTGGTCCAGTCAGCAGGGCAGCAAAGCAGACTACCCAGAGGGG  
GACGGCAACTGGGCCAACTACAACACCTTTGGATCTGCAGAGGCGGCCACGAGCGATGACTAC  
AAGAACCCTGGCTACTACGACATCCAGGCCAAGGACCTGGGCATCTGGCACGTGCCCAATAAG  
TCCCCCATGCAGCACTGGAGAAACAGCTCCCTGCTGAGGTACCGCACGGACACTGGCTTCCTC  
CAGACACTGGGACATAATCTGTTTGGCATCTACCAGAAATATCCAGTGAAATATGGAGAAGGA  
AAGTGTGGACTGACAACGGCCCCGGTGATCCCTGTGGTCTATGATTTTGGCGACGCCCAGAAA  
ACAGCATCTTATTACTCACCTATGGCCAGCGGGAATTCAGTGCGGGATTTGTTCAGTTTCAGG  
GTATTTAATAACGAGAGAGCAGCCAACGCCTTGTGTGCTGGAATGAGGGTCACCGGATGTAAC  
ACTGAGCATCACTGCATTGGTGGAGGAGGATACTTTCCAGAGGCCAGTCCCCAGCAGTGTGGA  
GATTTTCTGGTTTTGATTGGAGTGGATATGGAACATCATGTTGGTTACAGCAGCAGCCGTGAG  
ATAACTGAGGCAGCTGTGCTTCTATTCTATCGTTTGAGAGTTTTGTGGGAGGGAACCCAGACCT  
CTCCTCCCAACCATGAGATCCCAAGGATGGAGAACAACCTACCCAGTAGCTAGAATGTTAATG  
GCAGAAGAGAAAACAATAAATCATATTGACTCAAGAAAAAAA

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**FIGURE 88**

MNQLSFLLFLIATTRGWSTDEANTYFKEWTCSSSPSLPRSCKEIKDECPSAFDGLYFLRTENG  
VIYQTFCDMTSGGGGWTLVASVHENDMRGKCTVGDRWSSQQGSKADYPEGDGNWANYNTFGSA  
EAATSDDYKNPGYYDIQAKDLGIWHVPNKSPMQHWRNSSLLRYRTDTGFLQTLGHNLFGIYQK  
YPVKYGEKGCWTDNGPVI PVVYDFGDAQKTASYISPYGQREFTAGFVQFRVFNNERAANALCA  
GMRVTGCNTEHHCIGGGGYFPEASPPQCGDFSGFDWSGYGTHVGYSSSREITEAAVLLFYR

**Important features:****Signal peptide:**

amino acids 1-16

**N-glycosylation site.**

amino acids 163-167

**Glycosaminoglycan attachment sites.**

amino acids 74-78, 289-293

**N-myristoylation sites.**

amino acids 76-82, 115-121, 124-130, 253-259, 292-298

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**FIGURE 89**

CTAGATTTGTCGGCTTGCGGGGAGACTTCAGGAGTCGCTGTCTCTGAACTTCCAGCCTCAGAG  
ACCGCCGCCCTTGTCCTCCGAGGGCCATGGGCCGGGTCTCAGGGCTTGCGCCCTCTCGCTTCCT  
GACGCTCCTGGCGCATCTGGTGGTCGTCATCACCTTATTCTGGTCCCGGGACAGCAACATACA  
GGCCTGCCTGCCTCTCACGTTACCCCCGAGGAGTATGACAAGCAGGACATTCAGCTGGTGGC  
CGCGCTCTCTGTCACCCTGGGCCTCTTTGCAGTGGAGCTGGCCGGTTTCCTCTCAGGAGTCTC  
CATGTTCAACAGCACCCAGAGCCTCATCTCCATTGGGGCTCACTGTAGTGCATCCGTGGCCCT  
GTCCTTCTTCATATTCGAGCGTTGGGAGTGCACCTACGTATTGGTACATTTTTGTCTTCTGCAG  
TGCCCTTCCAGCTGTCACTGAAATGGCTTTATTCGTCACCGTCTTTGGGCTGAAAAAGAAACC  
CTTCTGATTACCTTCATGACGGGAACCTAAGGACGAAGCCTACAGGGGCAAGGGCCGCTTCGT  
ATTCCTGGAAGAAGGAAGGCATAGGCTTCGGTTTTCCCCTCGGAAACTGCTTCTGCTGGAGGA  
TATGTGTTGGAATAATTACGTCTTGAGTCTGGGATTATCCGCATTGTATTTAGTGCTTTGTAA  
TAAATATGTTTTGTAGTAACATTAAGACTTATATACAGTTTTAGGGGACAATTAAAAAAA  
AAA

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## **FIGURE 90**

MGRVSGLVPSRFLTLLAHLVVVITLFWSRDSNIQACLPLTFTPEEYDKQDIQLVAALSVTLGL  
FAVELAGFLSGVSMFNSTQSLISIGAHCSASVALSFFIFERWECTTYWYIFVFCSALPAVTEM  
ALFVTVFGLKKKPF

**Transmembrane domain:**

amino acids 12-28 (type II), 51-66, 107-124

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**FIGURE 91**

CTGGGACCCCGAAAAGAGAAGGGGAGAGCGAGGGGACGAGAGCGGAGGAGGAAG**ATGCA**ACTG  
ACTCGCTGCTGCTTCGTGTTTCCTGGTGCAGGGTAGCCTCTATCTGGTCATCTGTGGCCAGGAT  
GATGGTCCTCCCGGCTCAGAGGACCCTGAGCGTGATGACCACGAGGGCCAGCCCCGGCCCCGG  
GTGCCTCGGAAGCGGGGCCACATCTCACCTAAGTCCCGCCCCATGGCCAATTCCACTCTCCTA  
GGGCTGCTGGCCCCGCCTGGGGAGGCTTGGGGCATTCTTGGGCAGCCCCCAACCGCCCGAAC  
CACAGCCCCCACCCTCAGCCAAGGTGAAGAAAATCTTTGGCTGGGGCGACTTCTACTCCAAC  
ATCAAGACGGTGGCCCTGAACCTGCTCGTCACAGGGAAGATTGTGGACCATGGCAATGGGACC  
TTCAGCGTCCACTTCCAACACAATGCCACAGGCCAGGGAAACATCTCCATCAGCCTCGTGCCC  
CCCAGTAAAGCTGTAGAGTTCCACCAGGAACAGCAGATCTTCATCGAAGCCAAGGCCTCCAAA  
ATCTTCAACTGCCGGATGGAGTGGGAGAAGGTAGAACGGGGCCGCCGGACCTCGCTTTCACC  
CACGACCCAGCCAAGATCTGCTCCCGAGACCACGCTCAGAGCTCAGCCACCTGGAGCTGCTCC  
CAGCCCTTCAAAGTCGTCTGTGTCTACATCGCCTTCTACAGCACGGACTATCGGCTGGTCCAG  
AAGGTGTGCCCAGATTACAACCTACCATAGTGATACCCCCTACTACCCATCTGGG**TGA**CCCCGGG  
GCAGGCCACAGAGGCCAGGCCAGGGCTGGAAGGACAGGCCTGCCCATGCAGGAGACCATCTGG  
ACACCGGGCAGGGAAGGGGTGGGCCTCAGGCAGGGAGGGGGGTGGAGACGAGGAGATGCCAA  
GTGGGGCCAGGGCCAAGTCTCAAGTGGCAGAGAAAGGGTCCCAAGTGCTGGTCCCAACCTGAA  
GCTGTGGAGTGACTAGATCACAGGAGCACTGGAGGAGGAGTGGGCTCTCTGTGCAGCCTCACA  
GGGCTTTGCCACGGAGCCACAGAGAGATGCTGGGTCCCCGAGGCCTGTGGGCAGGCCGATCAG  
TGTGGCCCCAGATCAAGTCATGGGAGGAAGCTAAGCCCTTGGTTCTTGCCATCCTGAGGAAAG  
ATAGCAACAGGGAGGGGGAGATTTTCATCAGTGTGGACAGCCTGTCAACTTAGGATGGATGGCT  
GAGAGGGCTTCCTAGGAGCCAGTCAGCAGGGTGGGGTGGGGCCAGAGGAGCTCTCCAGCCCTG  
CCTAGTGGGCGCCCTGAGCCCCTTGTCGTGTGCTGAGCATGGCATGAGGCTGAAGTGGCAACC  
CTGGGGTCTTTGATGTCTTGACAGATTGACCATCTGTCTCCAGCCAGGCCACCCCTTTCCAAA  
ATTCCCTCTTCTGCCAGTACTCCCCCTGTACCACCCATTGCTGATGGCACACCCATCCTTAAG  
CTAAGACAGGACGATTGTGGTCCTCCACACTAAGGCCACAGCCCATCCGCGTGCTGTGTGTC  
CCTCTTCCACCCCAACCCCTGCTGGCTCCTCTGGGAGCATCCATGTCCCGGAGAGGGGTCCCT  
CAACAGTCAGCCTCACCTGTCAGACCGGGGTCTCCCGGATCTGGATGGCGCCGCCCTCTCAG  
CAGCGGGCACGGGTGGGGCGGGGCCGGGCCGAGAGCATGTGCTGGATCTGTTCTGTGTGTCT  
GTCTGTGGGTGGGGGGAGGGGAGGGAAGTCTTGTGAAACCGCTGATTGCTGACTTTTGTGTGA  
AGAATCGTGTTCTTGGAGCAGGAAATAAAGCTTGCCCCGGGGCA

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## **FIGURE 92**

MQLTRCCFVFLVQGSLYLVICGQDDGPPGSEDPERDDHEGQPRPRVPRKRGHISPKSRPMANS  
TLLGLLAPPGEAWGILGQPPNRPNHSPPPSAKVKKIFGWGDFYSNIKTVALNLLVTGKIVDHG  
NGTFSVHFQHNATGQGNISISLVPPSKAVEFHQEQQIFIEAKASKIFNCRMWEKVERGRRTS  
LCTHDPAKICSRDHAQSSATWSCSQPFKVVCVYIAFYSTDYRLVQKVCPDYNHSDTPYYPSG

### **Important features of the protein:**

#### **Signal peptide:**

amino acids 1-14

#### **N-glycosylation sites.**

amino acids 62-65, 127-130, 137-140, 143-146

#### **2-oxo acid dehydrogenases acyltransferase**

amino acids 61-71

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**FIGURE 93**

CGGTGGCC**ATG**ACTGCGGCCGTGTTCTTCGGCTGCGCCTTCATTGCCTTCGGGCCTGCGCTCG  
CCCTTTATGTCTTCACCATCGCCATCGAGCCGTTGCGTATCATCTTCCTCATCGCCGGAGCTT  
TCTTCTGGTTGGTGTCTCTACTGATTTTCGTCCCTTGTTTGGTTCATGGCAAGAGTCATTATTG  
ACAACAAAGATGGACCAACACAGAAATATCTGCTGATCTTTGGAGCGTTTGTCTCTGTCTATA  
TCCAAGAAATGTTCCGATTTGCATATTATAAACTCTTAAAAAAGCCAGTGAAGGTTTGAAGA  
GTATAAACCCAGGTGAGACAGCACCTCTATGCGACTGCTGGCCTATGTTTCTGGCTTGGGCT  
TTGGAATCATGAGTGGAGTATTTTCCTTTGTGAATACCTTATCTGACTCCTTGGGGCCAGGCA  
CAGTGGGCATTTCATGGAGATTCTCCTCAATTCTTCCTTTATTCAGCTTTCATGACGCTGGTCA  
TTATCTTGCTGCATGTATTCTGGGGCATTGTATTTTTTGTATGGCTGTGAGAAGAAAAAGTGGG  
GCATCCTCCTTATCGTTCTCCTGACCCACCTGCTGGTGTGAGCCAGACCTTCATAAGTTCTT  
ATTATGGAATAAACCTGGCGTCAGCATTTATAATCCTGGTGCTCATGGGCACCTGGGCATTCT  
TAGCTGCGGGAGGCAGCTGCCGAAGCCTGAACTCTGCCTGCTCTGCCAAGACAAGAACTTTC  
TTCTTTACAACCAGCGCTCCAGAT**TAA**CCTCAGGGAACCAGCACTTCCCAAACCGCAGACTACA  
TCTTTAGAGGAAGCACAACTGTGCCTTTTTCTGAAAATCCCTTTTTCTGGTGGAATTGAGAAA  
GAAATAAACTATGCAGATA

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**FIGURE 94**

MTAAVFFGCAFI AFGPALALYVFTIAIEPLRIIFLIAGAFFWLVSLLISSLVWFMARVIIDNK  
DGPTQKYLLIFGAFVSVYIQEMFRFAYYKLLKKASEGLKSINPGETAPSMRLLAYVSGLGFGI  
MSGVFSFVNTLSDSLPGTGVGIHGDSPQFFLYSAFMLVIILLHVFWGIVFFDGCEKKKWGIL  
LIVLLTHLLVSAQTFISSYYGINLASAFIILVLMGTWAF LAAGGSCRSLKCLLCQDKNFLLY  
NQRSR

**Important features of the protein:****Signal peptide:**

amino acids 1-19

**Transmembrane domains:**

amino acids 32-51, 119-138, 152-169, 216-235

**Glycosaminoglycan attachment site.**

amino acids 120-123

**Sodium:neurotransmitter symporter family protein**

amino acids 31-65



[illegible]

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## **FIGURE 96**

MRSTILLFCLLGSTRSLPQLKPALGLPPTKLAPDQGTLPNQQQSNQVFPSLSLIPLTQM  
LTLGPDHLNPAAGMTPGTQTHPLTLGGLNVQQQLHHPHVLPIFVTQLGAQGTLISSEE  
LPQIFETSLIIHSLFPGGILPTSQAGANPDVQDGSLPAGGAGVNPATQGTPAGRLPTPSG  
TDDDFAVTTPAGIQRSTHAIEEATTESANGIQ

**Signal peptide:**

amino acids 1-16

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**FIGURE 97**

GCTCAAGTGGCCCTGCCTTGCCCCACCCAGCCCAGCCTGGCCAGAGCCCCCTGGAGAAGGAGCT  
CTCTTCTTGCTTGGCAGCTGGACCAAGGGAGCCAGTCTTGGGCGCTGGAGGGCCTGTCTTGAC  
**CATGGT**CCCTGCCTGGCTGTGGCTGCTTTGTGTCTCCGTCCCCCAGGCTCTCCCCAAGGCCCA  
GCCTGCAGAGCTGTCTGTGGAAGTTCCAGAAAACCTATGGTGGAAATTTCCCTTTATACCTGAC  
CAAGTTGCCGCTGCCCCGTGAGGGGGCTGAAGGCCAGATCGTGCTGTCAGGGGACTCAGGCAA  
GGCAACTGAGGGGCCATTTGCTATGGATCCAGATTCTGGCTTCTGCTGGTGACCAGGGCCCT  
GGACCGAGAGGAGCAGGCAGAGTACCAGCTACAGGTCACCCTGGAGATGCAGGATGGACATGT  
CTTGTTGGGGTCCACAGCCTGTGCTTGTGCACGTGAAGGATGAGAATGACCAGGTGCCCCATTT  
CTCTCAAGCCATCTACAGAGCTCGGCTGAGCCGGGGTACCAGGCCTGGCATCCCCCTCCTCTT  
CCTTGAGGCTTCAGACCGGGATGAGCCAGGCACAGCCAACCTCGGATCTTCGATTCCACATCCT  
GAGCCAGGCTCCAGCCCAGCCTTCCCCAGACATGTTCCAGCTGGAGCCTCGGCTGGGGGCTCT  
GGCCCTCAGCCCCAAGGGGAGCACCAGCCTTGACCACGCCCTGGAGAGGACCTACCAGCTGTT  
GGTACAGGTCAAGGACATGGGTGACCAGGCCTCAGGCCACCAGGCCACTGCCACCGTGGAAGT  
CTCCATCATAGAGAGCACCTGGGTGTCCCTAGAGCCTATCCACCTGGCAGAGAATCTCAAAGT  
CCTATACCCGCACCACATGGCCCAGGTACACTGGAGTGGGGGTGATGTGCACTATCACCTGGA  
GAGCCATCCCCCGGGACCCCTTTGAAGTGAATGCAGAGGGAAACCTCTACGTGACCAGAGAGCT  
GGACAGAGAAGCCCAGGCTGAGTACCTGCTCCAGGTGCGGGCTCAGAATTCCCATGGCGAGGA  
CTATGCGGGCCCTCTGGAGCTGCACGTGCTGGTGATGGATGAGAATGACAACGTGCCTATCTG  
CCCTCCCCGTGACCCACAGTCAGCATCCCTGAGCTCAGTCCACCAGGTACTGAAGTGACTAG  
ACTGTCAGCAGAGGATGCAGATGCCCCCGGCTCCCCCAATTCCCACGTTGTGTATCAGCTCCT  
GAGCCCTGAGCCTGAGGATGGGGTAGAGGGGAGAGCCTTCCAGGTGGACCCCACTTCAGGCAG  
TGTGACGCTGGGGGTGCTCCCACTCCGAGCAGGCCAGAACATCCTGCTTCTGGTGCTGGCCAT  
GGACCTGGCAGGCGCAGAGGGTGGCTTCAGCAGCAGTGTGAAGTCGAAGTCGCAGTCACAGA  
TATCAATGATCAGCCCCCTGAGTTCATCACTTCCAGATTGGGCCTATAAGCCTCCCTGAGGA  
TGTGGAGCCCGGATCTGGTGCCCATGCTAACAGCCATTGATGCTGACCTCGAGCCCGCCTT  
CCGCCTCATGGATTTTGCCATTGAGAGGGGAGACACAGAAGGGACTTTTGGCCTGGATTGGGA  
GCCAGACTCTGGGCATGTTAGACTCAGACTCTGCAAGAACCTCAGTTATGAGGCAGCTCCAAG  
TCATGAGGTGGTGGTGGTGGTGCAGAGTGTGGCGAAGCTGGTGGGGCCAGGCCCAGGCCCTGG  
AGCCACCGCCACGGTGACTGTGCTAGTGGAGAGAGTGATGCCACCCCCCAAGTTGGACCAGGA  
GAGCTACGAGGCCAGTGTCCCCATCAGTGCCCCAGCCGGCTCTTTCCTGCTGACCATCCAGCC  
CTCCGACCCCATCAGCCGAACCCTCAGGTTCTCCCTAGTCAATGACTCAGAGGGCTGGCTCTG  
CATTGAGAAATTCTCCGGGGAGGTGCACACCGCCCAGTCCCTGCAGGGCGCCCAGCCTGGGGA  
CACCTACACGGTGCTTGTGGAGGCCCAGGATACAGCCCTGACTCTTGCCCCTGTGCCCTCCCA  
ATACCTCTGCACACCCCGCCAAGACCATGGCTTGATCGTGAGTGGACCCAGCAAGGACCCCGA  
TCTGGCCAGTGGGCACGGTCCCTACAGCTTACCCTTGGTCCCAACCCACGGTGCAACGGGA  
TTGGCGCCTCCAGACTCTCAATGGTTCCCATGCCTACCTCACCTTGGCCCTGCATTGGGTGGA  
GCCACGTGAACACATAATCCCCGTGGTGGTGCAGCCACAATGCCCAGATGTGGCAGCTCCTGGT  
TCGAGTGATCGTGTGTGCTGCAACGTGGAGGGGAGTGATGCGCAAGGTGGGCCGCATGAA  
GGGCATGCCACGAAGCTGTGCGCAGTGGGCATCCTTGTAGGCACCCTGGTAGCAATAGGAAT  
CTTCCTCATCCTCATTTTACCCACTGGACCATGTCAAGGAAGAAGGACCCGGATCAACCAGC  
AGACAGCGTGCCCTGAAGGCGACTGT**TGA**ATGGCCCAGGCAGCTCTAGCTGGGAGCTTGGC  
CTCTGGCTCCATCTGAGTCCCCTGGGAGAGAGCCCAGCACCCAAGATCCAGCAGGGGACAGGA  
CAGAGTAGAAGCCCCTCCATCTGCCCTGGGGTGGAGGCACCATCACCATCACCAGGCATGTCT  
GCAGAGCCTGGACACCAACTTTATGGACTGCCCATGGGAGTGCTCCAAATGTCAGGGTGTTTG  
CCCAATAATAAAGCCCCAGAGAACTGGGCTGGGCCCTATGGGAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAG

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**FIGURE 98**

MVPAWLWLLCVSVPQALPKAQP AELSVEVPENYGGNFPLYLTKLPLPREGAEGQIVLSGDSGK  
ATEGPFAMDPDSGFLLVTRALDREEQA EYQLQVTLEMQDGHVLWGPQPVLVHVKDENDQVPHF  
SQAIYRARLSRGTRPGIPFLFLEASDRDEPGTANSDLRFHILSQAPAQSPDMFQLEPRLGAL  
ALSPKGSTSLDHALERTYQLLVQVKDMGDQASGHQATATVEVSI IESTWVSLEPIHLAENLKV  
LYPHHMAQVHWSGGDVHYHLESHPPGPF EVNAEGNLYVTRELDREAQA EYLLQVRAQNSHGED  
YAAPLELHVLVMDENDNVPICPPRDPTVSIPELSPPGTEVTRL SAEDADAPGSPNSHVYQLL  
SPEPEDGVEGRAFQVDPTSGSVTLGVLPLRAGQNILLVLAMDLAGAEGGFSSTCEVEVAVTD  
INDHAPEFITSQIGPISLPEDVEPGTLVAMLT AIDADLEPAFRLMDFAIERGDT EGTGFLDWE  
PDSGHVRLRLCKNLSYEAAPSHEVVVVVQSVAKLVGPGPGGATATVTVLVERVMPPPKLDQE  
SYEASVPISAPAGSFLLTIQSPDPISR TLRFSLVNDSEGWLCIEKFSGEVHTAQSLQGAQPGD  
TYTVLVEAQDTALT LAPVPSQYLCTPRQDHGLIVSGPSKDPDLASGHGPYSFTLGNPTVQRD  
WRLQTLNGSHAYLTLALHWVEPREHII PVVVSHNAQMWQLLVRVIVCRCNVEGQCMRKVGRMK  
GMPTKLSAVGILVGT LVAIGIFLILIFTHWTMSRKKDPDQPADSVPLKATV

**Signal peptide:**

amino acids 1-18

**Transmembrane domain:**

amino acids 762-784

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**FIGURE 99**

GGCTGACCGTGCTACATTGCCTGGAGGAAGCCTAAGGAACCCAGGCATCCAGCTGCCCACGCC  
TGAGTCCAAGATTCTTCCCAGGAACACAAACGTAGGAGACCCACGCTCCTGGAAGCACCAGCC  
TTTATCTCTTCACCTTCAAGTCCCCTTTCTCAAGAATCCTCTGTTCTTTGCCCTCTAAAGTCT  
TGGTACATCTAGGACCCAGGCATCTTGCTTTCCAGCCACAAAGAGACAGATGAAGATGCAGAA  
AGGAAATGTTCTCCTTATGTTTTGGTCTACTATTGCATTTAGAAGCTGCAACAAATCCAATGA  
GACTAGCACCTCTGCCAACACTGGATCCAGTGTGATCTCCAGTGGAGCCAGCACAGCCACCAA  
CTCTGGGTCCAGTGTGACCTCCAGTGGGGTCCAGCACAGCCACCATCTCAGGGTCCAGCGTGAC  
CTCCAATGGGGTCCAGCATAGTCACCAACTCTGAGTTCATACAACCTCCAGTGGGATCAGCAC  
AGCCACCAACTCTGAGTTCAGCACAGCGTCCAGTGGGATCAGCATAGCCACCAACTCTGAGTC  
CAGCACAACCTCCAGTGGGGCCAGCACAGCCACCAACTCTGAGTCCAGCACACCTCCAGTGG  
GGCCAGCACAGTCACCAACTCTGGGTCCAGTGTGACCTCCAGTGGAGCCAGCACTGCCACCAA  
CTCTGAGTCCAGCACAGTGTCCAGTAGGGCCAGCACTGCCACCAACTCTGAGTCTAGCACACT  
CTCCAGTGGGGCCAGCACAGCCACCAACTCTGACTCCAGCACAACTCCAGTGGGGCTAGCAC  
AGCCACCAACTCTGAGTCCAGCACAACTCCAGTGGGGCCAGCACAGCCACCAACTCTGAGTC  
CAGCACAGTGTCCAGTAGGGCCAGCACTGCCACCAACTCTGAGTCCAGCACAACTCCAGTGG  
GGCCAGCACAGCCACCAACTCTGAGTCCAGAACGACCTCCAATGGGGCTGGCACAGCCACCAA  
CTCTGAGTCCAGCACGACCTCCAGTGGGGCCAGCACAGCCACCAACTCTGACTCCAGCACAGT  
GTCCAGTGGGGCCAGCACTGCCACCAACTCTGAGTCCAGCACGACCTCCAGTGGGGCCAGCAC  
AGCCACCAACTCTGAGTCCAGCACGACCTCCAGTGGGGCTAGCACAGCCACCAACTCTGACTC  
CAGCACAACCTCCAGTGGGGCCGGCACAGCCACCAACTCTGAGTCCAGCACAGTGTCCAGTGG  
GATCAGCACAGTCACCAATTCTGAGTCCAGCACACCTCCAGTGGGGCCAAACACAGCCACCAA  
CTCTGAGTCCAGTACGACCTCCAGTGGGGCCAAACACAGCCACCAACTCTGAGTCCAGCACAGT  
GTCCAGTGGGGCCAGCACTGCCACCAACTCTGAGTCCAGCACAACTCCAGTGGGGTCCAGCAC  
AGCCACCAACTCTGAGTCCAGCACAACTCCAGTGGGGCTAGCACAGCCACCAACTCTGACTC  
CAGCACAACCTCCAGTGGGGCCAGCACAGCCACCAACTCTGAGTCCAGTGTCCAGTGG  
GATCAGCACAGTCACCAATTCTGAGTCCAGCACAACTCCAGTGGGGCCAAACACAGCCACCAA  
CTCTGAGTCCAGTACGACCTCCAGTGGGGCCAAACACAGCCACCAACTCTGAGTCCAGCACAGT  
GTCCAGTGGGGCCAGCACTGCCACCAACTCTGAGTCCAGCACAACTCCAGTGGGGTCCAGCAC  
AGCCACCAACTCTGAGTCCAGCACAACTCCAGTGGGGCTAGCACAGCCACCAACTCTGACTC  
CAGCACAACCTCCAGTGGGGCCAGCACAGCCACCAACTCTGAGTCCAGTGTCCAGTGG  
GATCAGCACAGTCACCAATTCTGAGTCCAGCACAACTCCAGTGGGGCCAAACACAGCCACCAA  
CTCTGAGTCCAGTGTGACCTCTGCAGGCTCTGGAACAGCAGCTCTGACTGGAATGCACACAAC  
TTCCCATAGTGATCTACTGCAGTGTGAGGCAAAGCCTGGTGGGTCCCTGGTGCCGTGGGA  
AATCTTCCTCATCACCTGGTCTCGGTTGTGGCGGCCGTGGGGCTCTTTGCTGGGCTCTTCTT  
CTGTGTGAGAAACAGCCTGTCCCTGAGAAACACCTTTAACACAGCTGTCTACCACCCTCATGG  
CCTCAACCATGGCCTTGGTCCAGGCCCTGGAGGGAATCATGGAGCCCCCACAGGCCAGGTG  
GAGTCTTAAGTGGTTCTGGAGGAGACAGTATCATCGATAGCCATGGAGATGAGCGGGAGGAA  
CAGCGGGCCCAGAGCAGCCCCGGAAGCAAGTGGCGCATTCTTCAGGAAGGAAGAGACCTGGGC  
ACCAAGACCTGGTTTCCTTTTCATTCATCCCAGGAGACCCCTCCAGCTTTGTTTGAGATCCT  
GAAAATCTTGAAGAAGGTATTCCTCACCTTTCTGCCTTTACCAGACACTGGAAAGAGAATAC  
TATATTGCTCATTTAGCTAAGAAATAAATACATCTCATCTAACACACACGACAAAGAGAAGCT  
GTGCTTGCCCCGGGGTGGGTATCTAGCTCTGAGATGAACTCAGTTATAGGAGAAAACCTCCAT  
GCTGGACTCCATCTGGCATTCAAATCTCCACAGTAAATCCAAAGACCTCAAAAAAAAAAAAA  
AA

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**FIGURE 100**

MKMQKGNVLLMFGLLLHLEAATNSNETSTSANTGSSVISSGASTATNSGSSVTSSGVSTATIS  
GSSVTSNGVSIVTNSEFHTTSSGISTATNSEFSTASSGISIATNSESSTTSSGASTATNSESS  
TPSSGASTVTNSGSSVTSSGASTATNSESSTVSSRASTATNSESSTLSSGASTATNSDSSTTS  
SGASTATNSESSTTSSGASTATNSESSTVSSRASTATNSESSTTSSGASTATNSESRTTSNGA  
GTATNSESSTTSSGASTATNSDSSTVSSGASTATNSESSTTSSGASTATNSESSTTSSGASTA  
TNSDSSTTSSGAGTATNSESSTVSSGISTVTNSESSTPSSGANTATNSESSTTSSGANTATNS  
ESSTVSSGASTATNSESSTTSSGVSTATNSESSTTSSGASTATNSDSSTTSSEASTATNSESS  
TVSSGISTVTNSESSTTSSGANTATNSGSSVTSAGSGTAALTGMHTTSHSASTAVSEAKPGGS  
LVPWEIFLITLVSVVAAVGLFAGLFFCVRNSLSLRNTFNTAVYHPHGLNHGLGPGPGGNHGAP  
HRPRWSPNWFWRPVS SIAMEMSGRNSGP

**Signal peptide:**

amino acids 1-20

**Transmembrane domain:**

amino acids 510-532

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**FIGURE 101**

GGCCGGACGCCTCCGCGTTACGGGATGAATTAACGGCGGGTTCGCGACGGAGGTGTGACCCC  
TACGGAGCCCCAGCTTGCCACGCACCCCACTCGGCGTCGCGCGGCGTGCCCTGCTTGTCACA  
GGTGGGAGGCTGGAACATATCAGGCTGAAAAACAGAGTGGGTACTCTCTTCTGGGAAGCTGGCA  
ACAAATGGATGATGTGATATATGCATTCCAGGGGAAGGGAAATTGTGGTGCTTCTGAACCCAT  
GGTCAATTAACGAGGCAGTTTCTAGCTACTGCACGTACTTCATAAAGCAGGACTCTAAAAGCT  
TTGGAATCATGGTGTGTCATGGAAAGGGATTTACTTTATACTGACTCTGTTTTGGGGAAGCTTTT  
TTGGAAGCATTTTTCATGCTGAGTCCCTTTTTACCTTTGATGTTTGTAAACCCATCTTGGTATC  
GCTGGATCAACAACCGCCTTGTGGCAACATGGCTCACCCCTACCTGTGGCATTATTGGAGACCA  
TGTTTGGTGTAAGTGATTATAACTGGGGATGCATTTGTTTCTGGAGAAAGAAGTGTCATTA  
TCATGAACCATCGGACAAGAATGGACTGGATGTTTCTGTGGAATTGCCTGATGCGATATAGCT  
ACCTCAGATTGGAGAAAATTTGCCTCAAAGCGAGTCTCAAAGGTGTTCTGGATTTGGTTGGG  
CCATGCAGGCTGCTGCCTATATCTTCATTCATAGGAAATGGAAGGATGACAAGAGCCATTTTCG  
AAGACATGATTGATTACTTTTGTGATATTCACGAACCACTTCAACTCCTCATATTCCCAGAAG  
GGACTGATCTCACAGAAAACAGCAAGTCTCGAAGTAATGCATTTGCTGAAAAAATGGACTTC  
AGAAATATGAATATGTTTTACATCCAAGAACTACAGGCTTTACTTTTGTGGTAGACCGTCTAA  
GAGAAGGTAAGAACCTTGATGCTGTCCATGATATCACTGTGGCGTATCCTCACAACATTCCTC  
AATCAGAGAAGCACCTCCTCCAAGGAGACTTTCCCAGGGAAATCCACTTTCACGTCCACCGGT  
ATCCAATAGACACCCCTCCCCACATCCAAGGAGGACCTTCAACTCTGGTGCCACAAACGGTGGG  
AAGAGAAAGAAGAGAGGCTGCGTTCCTTCTATCAAGGGGAGAAGAATTTTTATTTTACCGGAC  
AGAGTGTCATTCCACCTTGCAAGTCTGAACTCAGGGTCCTTGTGGTCAAATTGCTCTCTATAC  
TGTATTGGACCCTGTTTCAGCCCTGCAATGTGCCTACTCATATATTTGTACAGTCTTGTTAAGT  
GGTATTTTATAATCACCATTGTAATCTTTGTGCTGCAAGAGAGAATATTTGGTGGACTGGAGA  
TCATAGAACTTGCAATGTTACCGACTTTTACACAAACAGCCACATTTAAATTCAAAGAAAAATG  
AGTAAGATTATAAGGTTTGCCATGTGAAAACCTAGAGCATATTTTGGAATGTTCTAAACCTT  
TCTAAGCTCAGATGCATTTTTGCATGACTATGTGCAATATTTCTTACTGCCATCATTATTTGT  
TAAAGATATTTTGCACCTTAATTTTGTGGGAAAAATATTGCTACAATTTTTTTTAAATCTCTGAA  
TGTAATTTTCGATACTGTGTACATAGCAGGGAGTGATCGGGGTGAAATAACTTGGGCCAGAATA  
TTATTAAACAATCATCAGGCTTTTAAA

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**FIGURE 102**

MHSRGREIVVLLNPWSINEAVSSYCTYFIKQDSKSGIMVSWKGIYFILTLFWGSFFGSIEML  
SPFLPLMFVNPSWYRWINNRLVATWLTLPVALLETMEFGVKVIITGDAFVPGERSVIIMNHRTR  
MDWMFLWNCLMRYSYLRLEKICLKASLKGVPFGFWAMQAAAYIFIHRKWKDDKSHFEDMIDYF  
CDIHEPLQLLIIFPEGTDLTENSKSRSNFAEKNGLQKYEYVLHPRTTGFTFVVDRLREGKNLD  
AVHDITVAYPHNIPQSEKHLLQGDFPREIHFHVHRYPIDTLPTSKEIDLQWCHKRWEEKEERL  
RSFYQGEKNFYFTGQSVIPPCKSELRVLVVKLLSILYWTLFSPAMCLLIYLYSLVKWYFIITI  
VIFVLQERIFGGLEIIELACYRLLHKQPHLNSKKNE

**Important features of the protein:****Signal peptide:**

amino acids 1-22

**Transmembrane domains:**

amino acids 44-63, 90-108, 354-377



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**FIGURE 103**

CGGCTCGAGCGGCTCGAGTGAAGAGCCTCTCCACGGCTCCTGCGCCTGAGACAGCTGGCCTGA  
CCTCCAAATCATCCATCCACCCCTGCTGTCTGTTTTCATAGTGTGAGATCAACCCACAGG  
AATATCCATGGCTTTTGTGCTCATTTTGGTTCTCAGTTTCTACGAGCTGGTGTGAGGACAGTG  
GCAAGTCACTGGACCGGGCAAGTTTGTCCAGGCCTTGGTGGGGGAGGACGCCGTGTTCTCCTG  
CTCCCTCTTTCTGAGACCAGTGCAGAGGCTATGGAAGTGCGGTTCTTCAGGAATCAGTTCCA  
TGCTGTGGTCCACCTCTACAGAGATGGGGAAGACTGGGAATCTAAGCAGATGCCACAGTATCG  
AGGGAGAACTGAGTTTGTGAAGGACTCCATTGCAGGGGGGCGTGTCTCTCTAAGGCTAAAAAA  
CATCACTCCCTCGGACATCGGCCTGTATGGGTGCTGGTTCAGTTCCCAGATTACGATGAGGA  
GGCCACCTGGGAGCTGCGGGTGGCAGCACTGGGCTCACTTCCTCTCATTTCCATCGTGGGATA  
TGTTGACGGAGGTATCCAGTTACTCTGCCTGTCTCAGGCTGGTTCCTCCAGCCACAGCCAA  
GTGGAAAGGTCCACAAGGACAGGATTTGTCTTCAGACTCCAGAGCAAATGCAGATGGGTACAG  
CCTGTATGATGTGGAGATCTCCATTATAGTCCAGGAAAATGCTGGGAGCATATTGTGTTCCAT  
CCACCTTGCTGAGCAGAGTCATGAGGTGGAATCCAAGGTATTGATAGGAGAGACGTTTTTCCA  
GCCCTCACCTTGCGCCTGGCTTCTATTTTACTCGGGTTACTCTGTGGTGCCCTGTGTGGTGT  
TGTCATGGGGATGATAATTGTTTTCTTCAAATCCAAAGGGAAAATCCAGGCCGAAGTGGACTG  
GAGAAGAAAGCACGGACAGGCAGAATTGAGAGACGCCCGGAAACACGCAGTGGAGGTGACTCT  
GGATCCAGAGACGGCTCACCCGAAGCTCTGCGTTTCTGATCTGAAAATGTAACCCATAGAAA  
AGCTCCCCAGGAGGTGCCTCACTCTGAGAAGAGATTTACAAGGAAGAGTGTGGTGGCTTCTCA  
GGGTTTCCAAGCAGGGAGACATTACTGGGAGGTGGACGTGGGACAAAATGTAGGGTGGTATGT  
GGGAGTGTGTCGGGATGACGTAGACAGGGGGAAGAACAATGTGACTTTGTCTCCCAACAATGG  
GTATTGGGTCTCAGACTGACAACAGAACATTTGTATTTACATTCAATCCCCATTTTATCAG  
CTCCCCCCCCAGCACCCCTCCTACACGAGTAGGGGTCTTCTTGACTATGAGGGTGGGACCAT  
CTCCTTCTTCAATACAAATGACCAGTCCCTTATTTATACCCTGCTGACATGTCAGTTTGAAGG  
CTTGTTGAGACCCTATATCCAGCATGCGATGTATGACGAGGAAAAGGGGACTCCCATATTCAT  
ATGTCCAGTGTCTTGGGGATGAGACAGAGAAGACCCTGCTTAAAGGGCCCCACACCACAGACC  
CAGACACAGCCAAGGGAGAGTGCTCCCCGACAGGTGGCCCCAGCTTCCTCTCCGGAGCCTGCGC  
ACAGAGAGTCACGCCCCCACTCTCCTTTAGGGAGCTGAGGTCTTCTGCCCTGAGCCCTGCA  
GCAGCGGCAGTCACAGCTTCAGATGAGGGGGGATTGGCCTGACCCTGTGGGAGTCAGAAGCC  
ATGGCTGCCCTGAAGTGGGGACGGAATAGACTCACATTAGGTTTAGTTTGTGAAAACCTCCATC  
CAGCTAAGCGATCTTGAACAAGTCACAACCTCCCAGGCTCCTCATTTGCTAGTCACGGACAGT  
GATTCCTGCCTCACAGGTGAAGATTAAAGAGACAACGAATGTGAATCATGCTTGAGGTTTGA  
GGGCACAGTGTGCTAATGATGTGTTTTTATATTATACATTTTCCCACCATAAACTCTGTTT  
GCTTATTCACATTAATTTACTTTTCTCTATACCAAATCACCCATGGAATAGTTATTGAACAC  
CTGCTTTGTGAGGCTCAAAGAATAAAGAGGAGTAGGATTTTTCACTGATTCTATAAGCCAG  
CATTACCTGATACCAAAAACCAGGCAAAGAAAACAGAAGAAGAGGAAGGAAAACCTACAGGTCCA  
TATCCCTCATTAACACAGACACAAAAATTTCTAAATAAAATTTTAACAAATTAACTAAACAAT  
ATATTTAAAGATGATATATACTACTCAGTGTGGTTTGTCCCACAAATGCAGAGTTGGTTTAA  
TATTTAAATATCAACCAGTGTAATTCAGCACATTAATAAAGTAAAAAAGAAAACCATAAAAAA  
AAAAAAA

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**FIGURE 104**

MAFVLILVLSFYELVSGWQVTGPGKFVQALVGEDAVFSCSLFPETSAEAMEVRFFRNQFHAV  
VHLYRDGEDWESKQMPQYRGRTEFVKDSIAGGRVSLRLKNITPSDIGLYGCWFSSQIYDEEAT  
WELRVAALGSLPLISIVGYVDGGIQLLCLSSGWFPQPTAKWKGPQGQDLSSDSRANADGYSLY  
DVEISIIVQENAGSILCSIHAEQSHEVESKVLIGETFFQPSWRLASILLGLLCGALCGVVM  
GMIIVFFKSKGKIQAELDWRRKHGQAELRDARKHAVEVTLDPETAHPKLCVSDLKTVTHRKAP  
QEVPHSEKRFTRKSVVASQGFQAGRHYWEVDVGQNVGWYVGVCRDDVDRGKNNVTLSPNNGYW  
VLRLTTEHLYFTFNPHFISLPPSTPPTRVGVFLDYEGGTISFFNTNDQSLIYTLLTCQFEGLL  
RPYIQHAMYDEEKGTPIFICPVSWG

**Signal peptide:**

amino acids 1-17

**Transmembrane domains:**

amino acids 131-150, 235-259

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**FIGURE 105**

CCTTCACAGGACTCTTCATTGCTGGTTGGCAATGATGTATCGGCCAGATGTGGTGAGGGCTAG  
GAAAAGAGTTTGTGGGAACCCTGGGTATCGGCCCTCGTCATCTTCATATCCCTGATTGTCTT  
GGCAGTGTGCATTGGACTCACTGTTTATTATGTGAGATATAATCAAAAGAAGACCTACAATTA  
CTATAGCACATTGTCAATTTACAACGACAACTATATGCTGAGTTTGGCAGAGAGGCTTCTAA  
CAATTTTACAGAAATGAGCCAGAGACTTGAATCAATGGTGAAAAATGCATTTTATAAATCTCC  
ATTAAGGGAAGAATTTGTCAAGTCTCAGGTTATCAAGTTCAGTCAACAGAAGCATGGAGTGTT  
GGCTCATATGCTGTTGATTTGTAGATTTCACTCTACTGAGGATCCTGAACTGTAGATAAAAT  
TGTTCAACTTGTTTTACATGAAAAGCTGCAAGATGCTGTAGGACCCCTAAAGTAGATCCTCA  
CTCAGTTAAATTAATAAATCAACAAGACAGAAACAGACAGCTATCTAAACCATTGCTGCGG  
AACACGAAGAAGTAAACTCTAGGTCAGAGTCTCAGGATCGTTGGTGGGACAGAAGTAGAAGA  
GGGTGAATGGCCCTGGCAGGCTAGCCTGCAGTGGGATGGGAGTCATCGCTGTGGAGCAACCTT  
AATTAATGCCACATGGCTTGTGAGTGCTGCTCACTGTTTTACAACATATAAGAACCCTGCCAG  
ATGGACTGCTTCCTTTGGAGTAACAATAAAACCTTCGAAAATGAAACGGGGTCTCCGGAGAAT  
AATTGTCCATGAAAAATACAAACACCCATCACATGACTATGATATTTCTCTTGACAGAGCTTTC  
TAGCCCTGTTCCCTACACAAATGCAGTACATAGAGTTTGTCTCCCTGATGCATCCTATGAGTT  
TCAACCAGGTGATGTGATGTTTGTGACAGGATTTGGAGCACTGAAAAATGATGGTTACAGTCA  
AAATCATCTTCGACAAGCACAGGTGACTCTCATAGACGCTACAACCTGCAATGAACCTCAAGC  
TTACAATGACGCCATAACTCCTAGAAATGTTATGTGCTGGCTCCTTAGAAGGAAAAACAGATGC  
ATGCCAGGGTGACTCTGGAGGACCACTGGTTAGTTCAGATGCTAGAGATATCTGGTACCTTGC  
TGGAATAGTGAGCTGGGGAGATGAATGTGCGAAACCCAACAAGCCTGGTGTTTATACTAGAGT  
TACGGCCTTGCGGGACTGGATTACTTCAAAAACCTGGTATCTAAGAGACAAAAGCCTCATGGAA  
CAGATAACATTTTTTTTTTGTTTTTTGGGTGTGGAGGCCATTTTATAGAGATACAGAATTGGAGA  
AGACTTGCAAAACAGCTAGATTTGACTGATCTCAATAAACTGTTTGCTTGATGCATGTATTTT  
CTTCCCAGCTCTGTTCCGCACGTAAGCATCCTGCTTCTGCCAGATCAACTCTGTCATCTGTGA  
GCAATAGTTGAACTTTATGTACATAGAGAAATAGATAATAACAATATTACATTACAGCCTGTA  
TTCATTTGTTCTCTAGAAGTTTTGTGAGAATTTGACTTGTTGACATAAATTTGTAATGCATA  
TATACAATTTGAAGCACTCCTTTTCTTCAGTTCCTCAGCTCCTCTCATTTTCAGCAAATATCCA  
TTTTCAAGGTGCAGAACAAAGGAGTGAAAGAAAATATAAGAAGAAAAAATCCCCTACATTTTA  
TTGGCACAGAAAAGTATTAGGTGTTTTTCTTAGTGGAATATTAGAAATGATCATATTCATTAT  
GAAAGGTCAAGCAAAGACAGCAGAATACCAATCACTTCATCATTTAGGAAGTATGGGAACATA  
GTTAAGGAAGTCCAGAAAGAAGCCAAGATATATCCTTATTTTCATTTCCAAACAACTACTATG  
ATAAATGTGAAGAAGATTCTGTTTTTTGTGACCTATAATAATTATACAAACTTCATGCAATG  
TACTTGTTCTAAGCAAATTAAGCAAATATTTATTTAACATTGTTACTGAGGATGTCAACATA  
TAACAATAAAATATAAATCACCCA

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**FIGURE 106**

MMYRPDVVRARKRVCWEPWVIGLVIFISLIVLAVCIGLTVHYVRYNQKKTYNYYSTLSFTTDK  
LYAEFGREASNNFTEMSQRLESMVKNAFYKSPLREEFVKSQVIKFSQQKHGVLAHMLLICRFH  
STEDPETVDKIVQLVLHEKLQDAVGPPKVDPHSVKIKKINKTETDSYLNHCCGTRRSKTLGQS  
LRIVGGTEVEEGEWPWQASLQWDGSHRCGATLINATWLVSAAHCFTTYKNPARWTASFGVTIK  
PSKMKRGLRRIIVHEKYKHPSHDYDISLAELSSPVPTYNAVHRVCLPDASYEFQPGDVMFVTG  
FGALKNDGYSQNHRLRQAQVTLIDATTCNEPQAYNDAITPRMLCAGSLEGKTDACQGDSGGPLV  
SSDARDIWYLAGIVSWGDECAKPNKPGVYTRVTALRDWITSKTGI

**Transmembrane domain:**

amino acids 21-40 (type II)

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**FIGURE 107**

AGAGAAAGAAGCGTCTCCAGCTGAAGCCAATGCAGCCCTCCGGCTCTCCGCGAAGAAGTTCCC  
TGCCCCGATGAGCCCCCGCGTGCGTCCCCGACTATCCCCAGGCGGGCGTGGGGCACCGGGCC  
CAGCGCCGACGATCGCTGCCGTTTTTGCCCTTGGGAGTAGGATGTGGTGAAAGGATGGGGCTTC  
TCCCTTACGGGGCTCACAAATGGCCAGAGAAGATTCCGTGAAGTGTCTGCGCTGCCTGCTCTAC  
GCCCTCAATCTGCTCTTTTGGTTAATGTCCATCAGTGTGTTGGCAGTTTCTGCTTGGATGAGG  
GACTACCTAAATAATGTTCTCACTTTAACTGCAGAAACGAGGGTAGAGGAAGCAGTCATTTTG  
ACTTACTTTCCTGTGGTTCATCCGGTCATGATTGCTGTGTTGCTGTTTCCTTATCATTGTGGGG  
ATGTTAGGATATTGTGGAACGGTGAAAAGAAATCTGTTGCTTCTTGCACTGGTACTTTGGAAGT  
TTGCTTGTCATTTTCTGTGTAGAACTGGCTTGTGGCGTTTGGACATATGAACAGGAACCTTATG  
GTTCCAGTACAATGGTCAGATATGGTCACCTTTGAAAGCCAGGATGACAAATTATGGATTACCT  
AGATATCGGTGGCTTACTCATGCTTGGAAATTTTTTTCAGAGAGAGTTTAAGTGCTGTGGAGTA  
GTATATTTCACTGACTGGTTGGAAATGACAGAGATGGACTGGCCCCCAGATTCCCTGCTGTGTT  
AGAGAAATCCCAGGATGTTCCAACAGGCCACCAGGAAGATCTCAGTGACCTTTATCAAGAG  
GGTTGTGGGAAGAAAATGTATTCCTTTTTTGAGAGGAACCAACAACCTGCAGGTGCTGAGGTTT  
CTGGGAATCTCCATTGGGGTGACACAAATCCTGGCCATGATTCTCACCATTACTCTGCTCTGG  
GCTCTGTATTATGATAGAAGGGAGCCTGGGACAGACCAAATGATGTCCTTGAAGAATGACAAC  
TCTCAGCACCTGTCTATGTCCTCAGTAGAACTGTTGAAACCAAGCCTGTCAAGAATCTTTGAA  
CACACATCCATGGCAAACAGCTTTAATACACACTTTGAGATGGAGGAGTTATAAAAAGAAATG  
TCACAGAAGAAAACCAAACTTGTTTTATTGGACTTGTGAATTTTTGAGTACATACTATGTG  
TTTCAGAAATATGTAGAAATAAAAATGTTGCCATAAAATAACACCTAAGCATATACTATTCTA  
TGCTTTAAATGAGGATGGAAAAGTTTCATGTCATAAGTCACCACCTGGACAATAATTGATGC  
CCTTAAATGCTGAAGACAGATGTCATACCCACTGTGTAGCCTGTGTATGACTTTTACTGAAC  
ACAGTTATGTTTTGAGGCAGCATGGTTTGATTAGCATTTCCGCATCCATGCAAACGAGTCACA  
TATGGTGGGACTGGAGCCATAGTAAAGGTTGATTTACTTCTACCAACTAGTATATAAAGTACT  
AATTAATGCTAACATAGGAAGTTAGAAAATACTAATAACTTTTATTACTCAGCGATCTATTC  
TTCTGATGCTAAATAAATTATATATCAGAAAACCTTCAATATTGGTGACTACCTAAATGTGAT  
TTTTGCTGGTTACTAAAATATTCTTACCCTTAAAAGAGCAAGCTAACACATTGTCTTAAGCT  
GATCAGGGATTTTTGTATATAAGTCTGTGTAAATCTGTATAATTCAAGTCGATTTCAGTTCT  
GATAATGTTAAGAATAACCATATGAAAAGGAAAATTTGTCCTGTATAGCATCATTATTTTTTA  
GCCTTTCCTGTTAATAAAGCTTTACTATTCTGTCTGGGCTTATATTACACATATAACTGTTA  
TTTAAATACTTAACCACTAATTTTTGAAAATTACCACTGTGATACATAGGAATCATTATTCAGA  
ATGTAGTCTGGTCTTTAGGAAGTATTAATAAGAAAATTTGCACATAACTTAGTTGATTCAGAA  
AGGACTTGTATGCTGTTTTTCTCCCAAATGAAGACTCTTTTTGACACTAAACACTTTTTAAAA  
AGCTTATCTTTGCCTTCTCCAAACAAGAAGCAATAGTCTCCAAGTCAATATAAATCTACAGA  
AAATAGTGTTCTTTTTCTCCAGAAAATGCTTGTGAGAATCATTAAAACATGTGACAATTTAG  
AGATTCTTTGTTTTATTTCCTGATTAATATACTGTGGCAAATTACACAGATTATTAATTTT  
TTTACAAGAGTATAGTATATTTATTTGAAATGGGAAAAGTGCATTTTACTGTATTTTGTGTAT  
TTTGTATTATTCTCAGAATATGGAAAGAAAATTAATGTGTCAATAAATATTTTCTAGAGAG  
TAA

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**FIGURE 108**

MAREDSVKCLRCLLYALNLLFWLMSISVLAVSAWMRDYLNNVLTTLTAETRVEEAVILTYFPVV  
HPVMIAVCCFLIIVGMLGYCGTVKRNLLLLAWYFGSLLVIFCVELACGVWVWYEQELMVPVQWS  
DMVTLKARMTNYGLPRYRWLTHAWNFFQREFKCCGVVYFTDWLEMTMDWPPDSCCVREFPGC  
SKQAHQEDLSPLYQEGCGKKMYSFLRGTKQLQVLRFLGISIGVTQILAMILTITLLWALYYDR  
REPGTDQMMSLKNDNSQHLSCPSVELLKPSLSRIFEHTSMANSFNTHFEMEEL

**Signal peptide:**

amino acids 1-33

**Transmembrane domains:**

amino acids 12-35, 57-86, 94-114, 226-248

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**FIGURE 109**

CCAAGGCCAGAGCTGTGGACACCTTATCCCACTCATCCTCATCCTCTTCTCTGATAAAGCCC  
CTACCAGTGCTGATAAAGTCTTTCTCGTGAGAGCCTAGAGGCCTTAAAAAAAAAAGTGCTTGA  
AAGAGAAGGGGACAAAGGAACACCAGTATTAAGAGGATTTTCCAGTGTTTCTGGCAGTTGGTC  
CAGAAGGATGCTCCATTCTGCTTCTCACCTGCCTCTTCATCACAGGCACCTCCGTGTCACC  
CGTGGCCCTAGATCCTTGTTCTGCTTACATCAGCCTGAATGAGCCCTGGAGGAACACTGACCA  
CCAGTTGGATGAGTCTCAAGGTCCTCCTCTATGTGACAACCATGTGAATGGGGAGTGGTACCA  
CTTCACGGGCATGGCGGGAGATGCCATGCCTACCTTCTGCATACCAGAAAACCACTGTGGAAC  
CCACGCACCTGTCTGGCTCAATGGCAGCCACCCCTAGAAAGGCGACGGCATTGTGCAACGCCA  
GGCTTGTGCCAGCTTCAATGGGAACCTGCTGTCTCTGGAACACCACGGTGGGAAGTCAAGGCTTG  
CCCTGGAGGCTACTATGTGTATCGTCTGACCAAGCCAGCGTCTGCTTCCACGTCTACTGTGG  
TCATTTTTATGACATCTGCGACGAGGACTGCCATGGCAGCTGCTCAGATACCAGCGAGTGCAC  
ATGCGCTCCAGGAACCTGTGCTAGGCCCTGACAGGCAGACATGCTTTGATGAAAATGAATGTGA  
GCAAAACAACGGTGGCTGCAGTGAGATCTGTGTGAACCTCAAAAACCTCCTACCGCTGTGAGTG  
TGGGGTTGGCCGTGTGCTAAGAAGTGATGGCAAGACTTGTGAAGACGTTGAAGGATGCCACAA  
TAACAATGGTGGCTGCAGCCACTCTTGCCCTGGATCTGAGAAAGGCTACCAGTGTGAATGTCC  
CCGGGGCCTGGTGTCTGTCTGAGGATAACCACACTTGCCAAGTCCCTGTGTTGTGCAAAATCAA  
TGCCATTGAAGTGAACATCCCCAGGGAGCTGGTTGGTGGCCTGGAGCTCTTCTGACCAACAC  
CTCCTGCCGAGGAGTGTCCAACGGCACCCATGTCAACATCCTCTTCTCTCAAGACATGTGG  
TACAGTGGTTCGATGTGGTGAATGACAAGATTGTGGCCAGCAACCTCGTGACAGGTCTACCCAA  
GCAGACCCCGGGGAGCAGCGGGGACTTCATCATCCGAACCAGCAAGCTGCTGATCCCGGTGAC  
CTGCGAGTTTCCACGCCTGTACACCATTTCTGAAGGATACGTTCCCAACCTTCGAAACTCCCC  
ACTGGAAATCATGAGCCGAAATCATGGGATCTTCCCATTCACTCTGGAGATCTTCAAGGACAA  
TGAGTTTGAAGAGCCTTACCAGGAAGCTCTGCCCACCCTCAAGCTTCGTGACTCCCTCTACTT  
TGGCATTGAGCCCGTGGTGCACGTGAGCGGCTTGGAAGCTTGGTGGAGAGCTGCTTTGCCAC  
CCCCACCTCCAAGATCGACGAGGTCTGAAATACTACCTCATCCGGGATGGCTGTGTTTCAGA  
TGACTCGGTAAAGCAGTACACATCCCGGGATCACCTAGCAAAGCACTTCCAGGTCCCTGTCTT  
CAAGTTTGTGGCCAAAGACCACAAGGAAGTGTCTGCACTGCCGGGTCTTGTCTGTGGAGT  
GTTGGACGAGCGTTCCCGCTGTGCCAGGGTTGCCACCGGCGAATGCGTCGTGGGGCAGGAGG  
AGAGGACTCAGCCGGTCTACAGGGCCAGACGCTAACAGGCGGCCCCGATCCGCATCGACTGGGA  
GGACTAGTTTCGTAGCCATACCTCGAGTCCCTGCATTGGACGGCTCTGCTCTTTGGAGCTTCTC  
CCCCACCGCCCTCTAAGAACATCTGCCAACAGCTGGGTTTCAGACTTCACACTGTGAGTTTCAG  
ACTCCCAGCACCAACTCACTCTGATTCTGGTCCATTCACTGGGCACAGGTCACAGCACTGCTG  
AACAATGTGGCCTGGGTGGGGTTTCATCTTTCTAGGGTTGAAAATAAACTGTCCACCCAGAA  
AGACACTACCCCATTTCCCTCATTTCTTTCTACACTTAAATACCTCGTGTATGGTGCAATC  
AGACCACAAAATCAGAAGCTGGGTATAATATTTCAAGTTACAAACCCTAGAAAAATTAAACAG  
TTACTGAAATTATGACTTAAATACCCAATGACTCCTTAAATATGTAAATTATAGTTATACCTT  
GAAATTTCAATTCAAATGCAGACTAATTATAGGGAATTTGGAAGTGTATCAATAAAACAGTAT  
ATAATTTT

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**FIGURE 110**

MPPFLLLTCLFITGTSVSPVALDPCSAYISLNEPWRNTDHLDESQGPPLCDNHVNGEWYHFT  
GMAGDAMPTFCIPENHCGTHAPVWLNGSHPLEGDGIVQRQACASFNGNCCLWNTTVEVKACPG  
GYVYVRLTKPSVCFHVYCGHFYDIDCEDCHGSCSDTSECTCAPGTVLGPDRQTCFDENECEQN  
NGGCSEICVNLKNSYRCECGVGRVLRSDGKTCEDEVEGCHNNNGGCSHSCLGSEKGYQCECPRG  
LVLSEDNHTCQVPVLCKSNAIEVNIPRELVGGLFLTLNTSCRGVSNATHVNILFSLKTCGTV  
VDVVNDKIVASNLVTGLPKQTPGSSGDFIIRTSKLLIPVTCEFPRLYTISEGYVPNLRNSPLE  
IMSRNHGIFPFTLEIFKDNFEFEOPYREALPTLKLRLDSLYFGIEPVVHVSGLESILVESCFATPT  
SKIDEVLKYYLIRDGCVSDDSVKQYTSRDHLAKHFQVPVFKFVGKDHKEVFLHCRVLVCGVLD  
ERSRCAQGCHRRMRRGAGGEDSAGLQGQTLTGGPPIRIDWED

**Important features of the protein:****Signal peptide:**

amino acids 1-16

**N-glycosylation sites.**

amino acids 89-93, 116-120, 259-263, 291-295, 299-303

**Tyrosine kinase phosphorylation sites.**

amino acids 411-418, 443-451

**N-myristoylation sites.**amino acids 226-232, 233-239, 240-246, 252-258, 296-302, 300-306,  
522-528, 531-537**Aspartic acid and asparagine hydroxylation site.**

amino acids 197-209

**ZP domain proteins.**

amino acids 431-457

**Calcium-binding EGF-like proteins.**

amino acids 191-212, 232-253



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**FIGURE 111**

GAGAGAGGCAGCAGCTTGCTCAGCGGACAAGGATGCTGGGCGTGAGGGACCAAGGCCTGCCCT  
GCACTCGGGCCTCCTCCAGCCAGTGCTGACCAGGGACTTCTGACCTGCTGGCCAGCCAGGACC  
TGTGTGGGGAGGCCCTCCTGCTGCCTTGGGGTGACAATCTCAGCTCCAGGCTACAGGGAGACC  
GGGAGGATCACAGAGCCAGCATGTTACAGGATCCTGACAGTGATCAACCTCTGAACAGCCTCG  
ATGTCAAACCCCTGCGCAAACCCCGTATCCCCATGGAGACCTTCAGAAAGGTGGGGATCCCCA  
TCATCATAGCACTACTGAGCCTGGCGAGTATCATCATTGTGGTTGTCCTCATCAAGGTGATTCT  
TGGATAAATACTACTTCCCTGCGGGCAGCCTCTCCACTTCATCCCGAGGAAGCAGCTGTGTG  
ACGGAGAGCTGGACTGTCCCTTGGGGGAGGACGAGGAGCACTGTGTCAAGAGCTTCCCCGAAG  
GGCCTGCAGTGGCAGTCCGCCTCTCCAAGGACCGATCCACACTGCAGGTGCTGGACTCGGCCA  
CAGGGAAGTGGTTCTCTGCCTGTTTCGACAACTTCACAGAAGCTCTCGCTGAGACAGCCTGTA  
GGCAGATGGGCTACAGCAGAGCTGTGGAGATTGGCCCAGACCAGGATCTGGATGTTGTTGAAA  
TCACAGAAAACAGCCAGGAGCTTCGCATGCGGAACTCAAGTGGGCCCTGTCTCTCAGGCTCCC  
TGGTCTCCCTGCACTGTCTTGCCTGTGGGAAGAGCCTGAAGACCCCCCGTGTGGTGGGTGGGG  
AGGAGGCCTCTGTGGATTCTTGGCCTTGGCAGGTGAGCATCCAGTACGACAAACAGCACGTCT  
GTGGAGGGAGCATCCTGGACCCCCACTGGGTCTCACGGCAGCCCACTGCTTCAGGAAACATA  
CCGATGTGTTCAACTGGAAGGTGCGGGCAGGCTCAGACAACTGGGCAGCTTCCCATCCCTGG  
CTGTGGCCAAGATCATCATCATTGAATTCAACCCCATGTACCCCAAAGACAATGACATCGCCC  
TCATGAAGCTGCAGTTCCCACTCACTTTCTCAGGCACAGTCAGGCCCATCTGTCTGCCCTTCT  
TTGATGAGGAGCTCACTCCAGCCACCCCACTCTGGATCATTGGATGGGGCTTTACGAAGCAGA  
ATGGAGGGAAGATGTCTGACATACTGCTGCAGGCGTCAGTCCAGGTCATTGACAGCACACGGT  
GCAATGCAGACGATGCGTACCAGGGGGAAGTCACCGAGAAGATGATGTGTGCAGGCATCCCGG  
AAGGGGGTGTGGACACCTGCCAGGGTGACAGTGGTGGGCCCCTGATGTACCAATCTGACCAGT  
GGCATGTGGTGGGCATCGTTAGCTGGGGCTATGGCTGCGGGGGCCCGAGCACCCAGGAGTAT  
ACACCAAGGTCTCAGCCTATCTCAACTGGATCTACAATGTCTGGAAGGCTGAGCTGTAATGCT  
GCTGCCCCCTTTGCAGTGCTGGGAGCCGCTTCCCTTCCCTGCCCTGCCACCTGGGGATCCCCCAA  
AGTCAGACACAGAGCAAGAGTCCCCTTGGGTACACCCCTCTGCCCACAGCCTCAGCATTTCTT  
GGAGCAGCAAAGGGCCTCAATTCCCTGTAAGAGACCCTCGCAGCCCAGAGGCGCCCAGAGGAAG  
TCAGCAGCCCTAGCTCGGCCACACTTGGTGCTCCCAGCATCCCAGGGAGAGACACAGCCCACT  
GAACAAGGTCTCAGGGGTATTGCTAAGCCAAGAAGGAACCTTCCCACACTACTGAATGGAAGC  
AGGCTGTCTTGTAAGAGCCAGATCACTGTGGGCTGGAGAGGAGAAGGAAAGGGTCTGCGCCA  
GCCCTGTCCGTCTTACCCATCCCCAAGCCTACTAGAGCAAGAAACCAGTTGTAATATAAAAT  
GCACTGCCCTACTGTTGGTATGACTACCGTTACCTACTGTTGTCATTGTTATTACAGCTATGG  
CCACTATTATTAAAGAGCTGTGTAACATCTCTGGCAAAAAAAAAAAAA

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**FIGURE 112**

MLQDPDSQPLNSLDVKPLRKPRIPMETFRKVGIPITIALLSLASIIIVVVLIKVILDKYYFL  
CGQPLHFIPRKQLCDGELDCPLGEDEEHCVKSFPEGPAVAVRLSKDRSTLQVLDSATGNWFSA  
CFDNFTEALAETACRQMGYSRAVEIGPDQDLVDVEITENSQELMRNSSGPCLSGSLVSLHCL  
ACGKSLKTPRVVGEEASVDSWPWQVSIQYDKQHVCSSILDPHWVLTAAHCFRKHTDVFNWK  
VRAGSDKLGSFPSLAVAKIIIIIEFNPMYPKDNDIALMKLQFPLTFSGTVRPICLPFFDEELTP  
ATPLWIIIGWGFTKQNGGKMSDILLQASVQVIDSTRCNADDAYQGEVTEKMMCAGIPEGGVDTG  
QGDSSGGLMYQSDQWHVVGIVSWGYGCGGPSTPGVYTKVSAYLNWIYNVWKAEL

**Transmembrane domain:**

amino acids 32-53 (typeII)

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**FIGURE 113**

GGCTGGACTGGAACCTCCTGGTCCCAAGTGATCCACCCGCCTCAGCCTCCCAAGGTGCTGTGAT  
TATAGGTGTAAGCCACCGTGTCTGGCCTCTGAACAACCTTTTTCAGCAACTAAAAAAGCCACAG  
GAGTTGAACTGCTAGGATTCTGACTATGCTGTGGTGGCTAGTGCTCCTACTCCTACCTACATT  
AAAATCTGTTTTTTGTTCTCTTGTAAGTACGCTTTACCTTCCTAACACAGAGGATCTGTCACT  
GTGGCTCTGGCCCAAACCTGACCTTCACTCTGGAACGAGAACAGAGGTTTCTACCCACACCGT  
CCCCTCGAAGCCGGGGACAGCCTCACCTTGCTGGCCTCTCGCTGGAGCAGTGCCCTCACCAAC  
TGTCTCACGTCTGGAGGCACTGACTCGGGCAGTGCAGGTAGCTGAGCCTCTTGGTAGCTGCGG  
CTTTCAAGGTGGGCCCTTGCCCTGGCCGTAGAAGGGATTGACAAGCCCGAAGATTTTCATAGGCG  
ATGGCTCCCACTGCCCAGGCATCAGCCTTGCTGTAGTCAATCACTGCCCTGGGGCCAGGACGG  
GCCGTGGACACCTGCTCAGAAGCAGTGGGTGAGACATCACGCTGCCCGCCCATCTAACCTTTT  
CATGTCCTGCACATCACCTGATCCATGGGCTAATCTGAACTCTGTCCCAAGGAACCCAGAGCT  
TGAGTGAGCTGTGGCTCAGACCCAGAAGGGGTCTGCTTAGACCACCTGGTTTATGTGACAGGA  
CTTGCAATTCTCCTGGAACATGAGGGAACGCCGGAGGAAAGCAAAGTGGCAGGGAAGGAACTTG  
TGCCAAATTATGGGTGAGAAAAGATGGAGGTGTTGGGTATCACAAAGGCATCGAGTCTCCTGC  
ATTCAGTGGACATGTGGGGGAAGGGCTGCCGATGGCGCATGACACACTCGGGACTCACCTCTG  
GGGCCATCAGACAGCCGTTTCCGCCCCGATCCACGTACCAGCTGCTGAAGGGCAACTGCAGGC  
CGATGCTCTCATCAGCCAGGCAGCAGCCAAAATCTGCGATCACCAGCCAGGGGCAGCCGTCTG  
GGAAGGAGCAAAGTGAACATTTCTCCTCCCCCTCCTTCCCTCTGAGAGGCCCTCCTATGT  
CCCTACTAAAGCCACCAGCAAGACATAGCTGACAGGGGCTAATGGCTCAGTGTTGGCCAGGA  
GGTCAGCAAGGCCTGAGAGCTGATCAGAAGGGCCTGCTGTGCGAACACGGAAATGCCTCCAGT  
AAGCACAGGCTGCAAAATCCCCAGGCAAAGGACTGTGTGGCTCAATTTAAATCATGTTCTAGT  
AATTGGAGCTGTCCCAAGACCAAAGGAGCTAGAGCTTGGTTCAAATGATCTCCAAGGGCCCT  
TATACCCAGGAGACTTTGATTTGAATTTGAAACCCCAAATCCAAACCTAAGAACCAGGTGCA  
TTAAGAATCAGTTATTGCCGGGTGTGGTGGCCTGTAATGCCAACATTTTGGGAGGCCGAGGCG  
GGTAGATCACCTGAGGTGAGGAGTTCAAGACCAGCCTGGCCAACATGGTGAAACCCCTGTCTC  
TACTAAAAATACAAAAAACTAGCCAGGCATGGTGGTGTGTGCCTGTATCCCAGCTACTCGGG  
AGGCTGAGACAGGAGAATTACTTGAACCTGGGAGGTGAAGGAGGCTGAGACAGGAGAATCACT  
TCAGCCTGAGCAACACAGCGAGACTCTGTCTCAGAAAAATAAAAAAGAATTATGGTTATTT  
GTAA

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## **FIGURE 114**

MLWWLVLLLLPTLKSVFCSLVTSLYLPNTEDLSLWLWPKPDLHSGTRTEVSTHTVPSKPGTAS  
PCWPLAGAVPSPTVSRLEALTRAVQVAEPLGSCGFQGGPCPGRRRD

**Signal peptide:**

amino acids 1-15

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**FIGURE 115**

CAGCAGTGGTCTCTCAGTCCTCTCAAAGCAAGGAAAGAGTACTGTGTGCTGAGAGACC**ATGGC**  
AAAGAATCCTCCAGAGAATTGTGAAGACTGTCACATTCTAAATGCAGAAGCTTTTAAATCCAA  
GAAAATATGTAAATCACTTAAGATTTGTGGACTGGTGTGTTGGTATCCTGGCCCTAACTCTAAT  
TGTCTGTTTTGGGGGAGCAAGCACTTCTGGCCGGAGGTACCCAAAAAAGCCTATGACATGGA  
GCACACTTTCTACAGCAATGGAGAGAAGAAGAAGATTTACATGGAAATTGATCCTGTGACCAG  
AACTGAAATATTCAGAAGCGGAAATGGCACTGATGAAACATTGGAAGTGCACGACTTTAAAAA  
CGGATACACTGGCATCTACTTCGTGGGTCTTCAAAAATGTTTTATCAAACTCAGATTAAAGT  
GATTCCTGAATTTTCTGAACCAGAAGAGGAAATAGATGAGAATGAAGAAATTACCACAACCTT  
CTTTGAACAGTCAGTGATTTGGGTCCCAGCAGAAAAGCCTATTGAAAACCGAGATTTTCTTAA  
AAATTCCAAAATTCTGGAGATTTGTGATAACGTGACCATGTATTGGATCAATCCCACTCTAAT  
ATCAGTTTCTGAGTTACAAGACTTTGAGGAGGAGGGAGAAGATCTTCACTTTCCTGCCAACGA  
AAAAAAGGGATTGAACAAAATGAACAGTGGGTGGTCCCTCAAGTGAAAGTAGAGAAGACCCG  
TCACGCCAGACAAGCAAGTGAGGAAGAAGCTTCCAATAAATGACTATACTGAAAATGGAATAGA  
ATTTGATCCCATGCTGGATGAGAGAGGTTATTGTTGTATTTACTGCCGTCGAGGCAACCGCTA  
TTGCCGCCGCGTCTGTGAACCTTTACTAGGCTACTACCCATATCCATACTGCTACCAAGGAGG  
ACGAGTCATCTGTCGTGTCATCATGCCTTGTAAGTGGTGGGTGGCCCGCATGCTGGGGAGGGT  
**CTAA**TAGGAGGTTTGAGCTCAAATGCTTAAACTGCTGGCAACATATAATAAATGCATGCTATT  
CAATGAATTTCTGCCTATGAGGCATCTGGCCCCTGGTAGCCAGCTCTCCAGAATTACTTGTAG  
GTAATTCCTCTCTTCATGTTCTAATAAACTTCTACATTATCACCAAAAAAAAAAAAAAAAAA

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**FIGURE 116**

MAKNPPENCEDCHILNAEAFKSKKICKSLKICGLVFGILALTILIVLFWGSKHFWPEVPPKAYD  
MEHTFYSNGEKKKIYMEIDPVTRTEIFRSGNGTDETLEVHDFKNGYTGIIYFVGLQKCFIKTQI  
KVIPEFSEPEEEIDENEEITTTFFEQSVIWWPAEKPIENRDFLKNSKILEICDNVTMYWINPT  
LISVSELQDFEEEGEDLHFPA NEKKGIEQNEQWVVPQVKVEKTRHARQASEEELPINDYTENG  
IEFDPM LDERGYCCIIYCRGNRYCRRVCEPLLGYYPYPYCYQGGRVICRVIMPCNWWVARMLGRV

**Important features of the protein:****Signal peptide:**

amino acids 1-40

**Transmembrane domain:**

amino acids 25-47 (type II)

**N-glycosylation sites.**

amino acids 94-97, 180-183

**Glycosaminoglycan attachment sites.**

amino acids 92-95, 70-73, 85-88, 133-136, 148-151, 192-195, 239-242

**N-myristoylation sites.**

amino acids 33-38, 95-100, 116-121, 215-220, 272-277

**Microbodies C-terminal targeting signal.**

amino acids 315-317

**Cytochrome c family heme-binding site signature.**

amino acids 9-14

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**FIGURE 117**

GAGCTCCCCTCAGGAGCGCGTTAGCTTCACACCTTCGGCAGCAGGAGGGCGGCAGCTTCTCGC  
AGGCGGCAGGGCGGGCGGCCAGGATCATGTCACCACCACATGCCAAGTGGTGGCGTTCCTCC  
TGTCCATCCTGGGGCTGGCCGGCTGCATCGCGGCCACCGGGATGGACATGTGGAGCAGCCAGG  
ACCTGTACGACAACCCCGTCACCTCCGTGTTCCAGTACGAAGGGCTCTGGAGGAGCTGCGTGA  
GGCAGAGTTCAGGCTTCACCGAATGCAGGGCCCTATTTACCATCCTGGGACTTCCAGCCATGC  
TGCAGGCAGTGCAGGCCCTGATGATCGTAGGCATCGTCCTGGGTGCCATTGGCCTCCTGGTAT  
CCATCTTTGCCCTGAAATGCATCCGCATTGGCAGCATGGAGGACTCTGCCAAAGCCAACATGA  
CACTGACCTCCGGGATCATGTTCAATTGTCTCAGGTCTTTGTGCAATTGCTGGAGTGTCTGTGT  
TTGCCAACATGCTGGTGACTAACTTCTGGATGTCCACAGCTAACATGTACACCGGCATGGGTG  
GGATGGTGCAGACTGTTAGACCAGGTACACATTTGGTGCGGCTCTGTTTCGTGGGCTGGGTG  
CTGGAGGCCTCACACTAATTGGGGGTGTGATGATGTGCATCGCCTGCCGGGGCCTGGCACCAG  
AAGAAACCAACTACAAAGCCGTTTCTTATCATGCCTCAGGCCACAGTGTTGCCTACAAGCCTG  
GAGGCTTCAAGGCCAGCACTGGCTTTGGGTCCAACACCAAAAACAAGAAGATATACGATGGAG  
GTGCCCCGCACAGAGGACGAGGTACAATCTTATCCTTCCAAGCACGACTATGTGTAAATGCTCTA  
AGACCTCTCAGCACGGGCGGAAGAACTCCCGGAGAGCTCACCAAAAAACAAGGAGATCCCA  
TCTAGATTTCTTCTTGCTTTTGACTCACAGCTGGAAGTTAGAAAAGCCTCGATTTTCATCTTTG  
GAGAGGCCAAATGGTCTTAGCCTCAGTCTCTGTCTCTAAATATTCCACCATAAAACAGCTGAG  
TTATTTATGAATTAGAGGCTATAGCTCACATTTTCAATCCTCTATTTCTTTTTTAAATATAA  
CTTTCTACTCTGATGAGAGAATGTGGTTTTAATCTCTCTCTCACATTTTGATGATTTAGACAG  
ACTCCCCCTCTTCTCCTAGTCAATAAACCCATTGATGATCTATTTCCCAGCTTATCCCCAAG  
AAAACTTTTGAAAGGAAAGAGTAGACCCAAAGATGTTATTTCTGCTGTTTGAATTTGTCTC  
CCCACCCCCAACTTGGCTAGTAATAAACACTTACTGAAGAAGAAGCAATAAGAGAAAGATATT  
TGTAATCTCTCCAGCCCATGATCTCGGTTTTCTTACACTGTGATCTTAAAAGTTACCAAACCA  
AAGTCATTTTCAGTTTGAGGCAACCAAACCTTTCTACTGCTGTTGACATCTTCTTATTACAGC  
AACACCATTCTAGGAGTTTCTGAGCTCTCCACTGGAGTCCTCTTCTGTGCGGGTCAGAAA  
TTGTCCCTAGATGAATGAGAAAAATTATTTTTTTTAATTTAAGTCCTAAATATAGTTAAAATAA  
ATAATGTTTTAGTAAATGATACACTATCTCTGTGAAATAGCCTCACCCCTACATGTGGATAG  
AAGGAAATGAAAAATAATTGCTTTGACATTGTCTATATGGTACTTTGTAAAGTCATGCTTAA  
GTACAAATTCCATGAAAAGCTCACACCTGTAATCCTAGCACTTTGGGAGGCTGAGGAGGAAGG  
ATCACTTGAGCCCAGAAGTTCGAGACTAGCCTGGGCAACATGGAGAAGCCCTGTCTCTACAAA  
ATACAGAGAGAAAAAATCAGCCAGTCATGGTGGCATAACCTGTAGTCCCAGCATTCGGGGAG  
GCTGAGGTGGGAGGATCACTTGAGCCCAGGGAGGTGGGGCTGCAGTGAGCCATGATCACACC  
ACTGCACTCCAGCCAGGTGACATAGCGAGATCCTGTCTAAAAAAATAAAAAATAAATAATGGA  
ACACAGCAAGTCCTAGGAAGTAGGTTAAACTAATTCTTTAA

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## **FIGURE 118**

MSTTTCQVVAFLLSILGLAGCIAATGMDMWSTQDLYDNPVTSVFQYEGLRSCVRQSSGFTEC  
RPYFTILGLPAMLQAVRALMIVGIVLGAIGLLVSIFALKCIRIGSMEDSAKANMTLTSGIMFI  
VSGLCAIAGVSVFANMLVTNFWMSTANMYTGMGGMVQTVQTRYTFGAALFVGWVAGGLTLIGG  
VMMCIACRGLAPEETNYKAVSYHASGHSVAYKPGGFKASTGFGSNTKNKKIYDGGARTEDEVQ  
SYPSKHDYV

**Signal peptide:**

amino acids 1-23

**Transmembrane domains:**

amino acids 81-100, 121-141, 173-194



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**FIGURE 119**

GGAAAACTGTTCTCTTCTGTGGCACAGAGAACCCTGCTTCAAAGCAGAAGTAGCAGTTCCGG  
AGTCCAGCTGGCTAAAACTCATCCCAGAGGATAATGGCAACCCATGCCTTAGAAATCGCTGGG  
CTGTTTCTTGGTGGTGTGGGAATGGTGGGCACAGTGGCTGTCACTGTCATGCCTCAGTGGAGA  
GTGTCGGCCTTCATTGAAAACAACATCGTGGTTTTTGAAAACCTCTGGGAAGGACTGTGGATG  
AATTGCGTGAGGCAGGCTAACATCAGGATGCAGTGCAAAATCTATGATTCCCTGCTGGCTCTT  
TCTCCGGACCTACAGGCAGCCAGAGGACTGATGTGTGCTGCTTCCGTGATGTCCTTCTTGGCT  
TTCATGATGGCCATCCTTGGCATGAAATGCACCAGGTGCACGGGGGACAATGAGAAGGTGAAG  
GCTCACATTCTGCTGACGGCTGGAATCATCTTCATCATCACGGGCATGGTGGTGCTCATCCCT  
GTGAGCTGGGTGCGCAATGCCATCATCAGAGATTTCTATAACTCAATAGTGAATGTTGCCCAA  
AAACGTGAGCTTGGAGAAGCTCTCTACTTAGGATGGACCACGGCACTGGTGCTGATTGTTGGA  
GGAGCTCTGTTCTGCTGCGTTTTTTGTTGCAACGAAAAGAGCAGTAGCTACAGATACTCGATA  
CCTTCCCATCGCACAAACCCAAAAAAGTTATCACACCGGAAAGAAGTCACCGAGCGTCTACTCC  
AGAAGTCAGTATGTGTAGTTGTGTATGTTTTTTTAACTTTACTATAAAGCCATGCAAATGACA  
AAAATCTATATTACTTTCTCAAAATGGACCCCAAAGAACTTTGATTTACTGTTCTTAACTGC  
CTAATCTTAATTACAGGAACTGTGCATCAGCTATTTATGATTCTATAAGCTATTTACAGCAGAA  
TGAGATATTAAACCAATGCTTTGATTGTTCTAGAAAGTATAGTAATTTGTTTTCTAAGGTGG  
TTCAAGCATCTACTCTTTTTATCATTTACTTCAAAATGACATTGCTAAAGACTGCATTATTTT  
ACTACTGTAATTTCTCCACGACATAGCATTATGTACATAGATGAGTGTAAACATTTATATCTCA  
CATAGAGACATGCTTATATGGTTTTATTTAAAATGAAATGCCAGTCCATTACACTGAATAAAT  
AGAACTCAACTATTGCTTTTCAGGGAAATCATGGATAGGGTTGAAGAAGGTTACTATTAATTG  
TTTAAAAACAGCTTAGGGATTAAATGTCCTCCATTTATAATGAAGATTAAAATGAAGGCTTTAA  
TCAGCATTGTAAAGGAAATTGAATGGCTTTCTGATATGCTGTTTTTTAGCCTAGGAGTTAGAA  
ATCCTAACTTCTTTATCCTCTTCTCCAGAGGCTTTTTTTTTCTTGTGTATTAAATTAACATT  
TTTAAAACGCAGATATTTTGTCAAGGGGCTTTGCATTCAAACCTGCTTTTCCAGGGCTATACTC  
AGAAGAAAGATAAAAGTGTGATCTAAGAAAAAGTGATGGTTTTTAGGAAAGTGAAAAATTTTTT  
GTTTTTGTATTTGAAGAAGAATGATGCATTTTGACAAGAAATCATATATGTATGGATATATTT  
TAATAAGTATTTGAGTACAGACTTTGAGGTTTCATCAATATAAATAAAAGAGCAGAAAAATAT  
GTCTTGGTTTTCATTTGCTTACCAAAAAACAACAACAAAAAAGTTGTCCTTTGAGAACTTC  
ACCTGCTCCTATGTGGGTACCTGAGTCAAATGTGCATTTTTGTTCTGTGAAAAATAAATTTT  
CTTCTTGTACCATTTCTGTTTAGTTTTACTAAAATCTGTAAATACTGTATTTTTCTGTTTATT  
CCAAATTTGATGAAACTGACAATCCAATTTGAAAGTTTGTGTGCGACGTCTGTCTAGCTTAAAT  
GAATGTGTTCTATTTGCTTTATACATTTATATTAATAAATTGTACATTTTTCTAATT

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## **FIGURE 120**

MATHALEIAGLFLGGVGMVGTVAVTVMQPWRVSAFIENNIVVFENFW EGLWMNCVRQANIRMQ  
CKIYDSL LALSPDLQAARGLMCAASVMSFLAFMMAILGMKCTRCTGDNEKVKAHILLTAGIIF  
IITGMVVLIPVSWVANAIIRDFYNSIVNVAQKRELGEALYLGWTTALVLIVGGALFCCVFCCN  
EKSSSYRYSIPSHRTTQKSYHTGKKSPSVYSRSQYV

**Signal peptide:**

amino acids 1-17

**Transmembrane domains:**

amino acids 82-101, 118-145, 164-188

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**FIGURE 121**

GGAGAGAGGCGCGCGGGTGAAAGGCGCATTGATGCAGCCTGCGGCGGCCTCGGAGCGCGGCGG  
AGCCAGACGCTGACCACGTTCCCTCTCCTCGGTCTCCTCCGCCTCCAGCTCCGCGCTGCCCGGC  
AGCCGGGAGCCATGCGACCCCAGGGCCCCGCCGCCTCCCCGCAGCGGCTCCGCGGCCTCCTGC  
TGCTCCTGCTGCTGCAGCTGCCCGCGCCGTCGAGCGCCTCTGAGATCCCCAAGGGGAAGCAAA  
AGGCGCAGCTCCGGCAGAGGGAGGTGGTGGACCTGTATAATGGAATGTGCTTACAAGGGCCAG  
CAGGAGTGCCTGGTCGAGACGGGAGCCCTGGGGCCAATGTTATTCCGGGTACACCTGGGATCC  
CAGGTCCGGATGGATTCAAAGGAGAAAAGGGGGAATGTCTGAGGGAAAGCTTTGAGGAGTCCT  
GGACACCCAACTACAAGCAGTGTTCATGGAGTTCATTGAATTATGGCATAGATCTTGGGAAAA  
TTGCGGAGTGTACATTTACAAAGATGCGTTCAAATAGTGCTCTAAGAGTTTTGTTCAAGTGGCT  
CACTTCGGCTAAAATGCAGAAATGCATGCTGTCAGCGTTGGTATTTACATTCAATGGAGCTG  
AATGTTCAAGACCTCTTCCCATTGAAGCTATAATTTATTTGGACCAAGGAAGCCCTGAAATGA  
ATTCAACAATTAATATTCATCGCACTTCTTCTGTGGAAGGACTTTGTGAAGGAATTGGTGCTG  
GATTAGTGGATGTTGCTATCTGGGTTGGCACTTGTTTCAGATTACCCAAAAGGAGATGCTTCTA  
CTGGATGGAATTCAGTTTCTCGCATCATTATTGAAGAACTACCAAAATAAATGCTTTAATTTT  
CATTTGCTACCTCTTTTTTTTATTATGCCTTGGAATGGTTCACTTAAATGACATTTTAAATAAG  
TTTATGTATACATCTGAATGAAAAGCAAAGCTAAATATGTTTACAGACCAAAGTGTGATTTCA  
CACTGTTTTTTAAATCTAGCATTATTCATTTTGCTTCAATCAAAGTGGTTTCAATATTTTTTT  
TAGTTGGTTAGAATACTTTCTTCATAGTCACATTCTCTCAACCTATAATTTGGAATATTGTTG  
TGGTCTTTTGTTTTTTCTCTTAGTATAGCATTTTTTAAAAAATATAAAAGCTACCAATCTTTG  
TACAATTTGTAAATGTTAAGAATTTTTTTTATATCTGTAAATAAAAAATTATTTCCAACA

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**FIGURE 122**

MRPQGPAASPQRLRGLLLLLLLQLPAPSSASEIPKGKQKAQLRQREVVDLYNGMCLQGPAAGVP  
GRDGSPGANVIPGTPGIPGRDGFKEKGECLRESFEESWTPNYKQCSWSSLNYGIDLKIAEC  
TFTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECSGPLPIEAIYLDQGSPEMNSTI  
NIHRTSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNSVSRIIIIEELPK

**Signal peptide:**

amino acids 1-30

**Transmembrane domain:**

amino acids 195-217

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**FIGURE 123**

GCTGAGCGTGTGCGCGGTACGGGGCTCTCCTGCCTTCTGGGCTCCAACGCAGCTCTGTGGCTG  
AACTGGGTGCTCATCACGGGAACCTGCTGGGCTATGGAATACAGATGTGGCAGCTCAGGTAGCC  
CCAAATTGCCTGGAAGAATACATCATGTTTTTCGATAAGAAGAAATTGTAGGATCCAGTTTTT  
TTTTTAACCGCCCCCTCCCCACCCCCCAAAAAAAGCTGTAAAGATGCAAAAACGTAATATCCAT  
GAAGATCCTATTACCTAGGAAGATTTTGATGTTTTGCTGCGAATGCGGTGTTGGGATTTATTT  
GTTCTTGGAGTGTTCTGCGTGGCTGGCAAAGAATAATGTTCCAAAATCGGTCCATCTCCCAAG  
GGGTCCAATTTTTCTTCTGGGTGTCAGCGAGCCCTGACTCACTACAGTGCAGCTGACAGGGG  
CTGTCATGCAACTGGCCCCCTAAGCCAAAGCAAAAGACCTAAGGACGACCTTTGAACAATACAA  
AGGATGGGTTTCAATGTAATTAGGCTACTGAGCGGATCAGCTGTAGCACTGGTTATAGCCCCC  
ACTGTCTTACTGACAATGCTTTCTTCTGCCGAACGAGGATGCCCTAAGGGCTGTAGGTGTGAA  
GGCAAATGGTATATTGTGAATCTCAGAAATTACAGGAGATACCCTCAAGTATATCTGCTGGT  
TGCTTAGGTTTGTCCCTTCGCTATAACAGCCTTCAAAAACCTTAAGTATAATCAATTTAAAGGG  
CTCAACCAGCTCACCTGGCTATACCTTGACCATAACCATATCAGCAATATTGACGAAAATGCT  
TTTAATGGAATACGCAGACTCAAAGAGCTGATTCTTAGTTCCAATAGAATCTCCTATTTTCTT  
AACAATACCTTCAGACCTGTGACAAATTTACGGAACTTGGATCTGTCTTATAATCAGCTGCAT  
TCTCTGGGATCTGAACAGTTTCGGGGCTTGCGGAAGCTGCTGAGTTTACATTTACGGTCTAAC  
TCCCTGAGAACCATCCCTGTGCGAATATTCCAAGACTGCCGCAACCTGGAACCTTTGGACCTG  
GGATATAACCGGATCCGAAGTTTAGCCAGGAATGCTTTGCTGGCATGATCAGACTCAAAGAA  
CTTCACCTGGAGCACAATCAATTTTCCAAGCTCAACCTGGCCCTTTTCCAAGGTTGGTCAGC  
CTTCAGAACCTTTACTTGCAGTGGAATAAAATCAGTGTATAGGACAGACCATGTCCTGGACC  
TGGAGCTCCTTACAAAGGCTTGATTTATCAGGCAATGAGATCGAAGCTTTCAGTGGACCCAGT  
GTTTTCCAGTGTGTCCCGAATCTGCAGCGCCTCAACCTGGATTCCAACAAGCTCACATTTATT  
GGTCAAGAGATTTTGGATTCTTGGATATCCCTCAATGACATCAGTCTTGCTGGGAATATATGG  
GAATGCAGCAGAAATATTTGCTCCCTTGTAAGCTGGCTGAAAAGTTTTAAAGGTCTAAGGGAG  
AATACAATTATCTGTGCCAGTCCCAAAGAGCTGCAAGGAGTAAATGTGATCGATGCAGTGAAG  
AACTACAGCATCTGTGGCAAAAGTACTACAGAGAGGTTTGATCTGGCCAGGGCTCTCCCAAAG  
CCGACGTTTAAGCCCAAGCTCCCCAGGCCGAAGCATGAGAGCAAACCCCTTTGCCCCCGACG  
GTGGGAGCCACAGAGCCCGGCCAGAGACCGATGCTGACGCCGAGCACATCTCTTCCATAAA  
ATCATCGCGGGCAGCGTGGCGCTTTTCCTGTCCGTGCTCGTCATCCTGCTGGTTATCTACGTG  
TCATGGAAGCGGTACCCTGCGAGCATGAAGCAGCTGCAGCAGCGCTCCCTCATGCGAAGGCAC  
AGGAAAAAGAAAAGACAGTCCCTAAAGCAAATGACTCCCAGCACCCAGGAATTTTATGTAGAT  
TATAAACCCACCAACACGGAGACCAGCGAGATGCTGCTGAATGGGACGGGACCCCTGCACCTAT  
AACAAATCGGGCTCCAGGGAGTGTGAGGTATGAACCATTTGTGATAAAAAGAGCTCTTAAAGC  
TGGGAAATAAGTGGTGCTTTATTGAACTCTGGTGACTATCAAGGGAACGCGATGCCCCCCTC  
CCCTTCCCTCTCCCTCTCACTTTGGTGGCAAGATCCTTCCTTGTCGGTTTTAGTGCATTCATA  
ATACTGGTCATTTTCCTCTCATACATAATCAACCCATTGAAATTTAAATACCACAATCAATGT  
GAAGCTTGAACCTCCGGTTTAATATAATACCTATTGTATAAGACCCTTTACTGATTCCATTAAT  
GTCGCATTTGTTTTAAGATAAAACTTCTTTCATAGGTAATAAAAAAAAAA

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**FIGURE 124**

MGFNVIRLLSGSAVALVIAPTVLLTMLSSAERGCPKGCRCGKMVYCESQKLQEIPSSISAGC  
LGLSLRYNSLQKLKYNQFKGLNQLTWLYLDHNHISNIDENAFNGIRRLKELILSSNRISYFLN  
NTERPVTNLRNLDLSYNQLHSLGSEQFRGLRKLLSLHLRSNSLRTIPVRIFQDCRNLELLDLG  
YNRIRSLARNVVFAGMIRLKEHLEHNQFSKLNLALEFRLVSLQONLYLQWNKISVIGQTMSWTW  
SSLQRLDLSGNEIEAFSGPSVFQCVPNLQRLNLDNSNKLTFIGQEILDSWISLNDISLAGNIWE  
CSRNICSLVNWLKSFKGLRENTIICASPKELQGVNVIDAVKNYSICGKSTTERFDLARALPKP  
TFKPKLPRPKHESKPPLPPTVGATEPGPETDADAEHISFHKI IAGSVALFLSVLVILLVIYVS  
WKRYPASMKQLQQRSLMRRHRKKRQSLKQMTPTSTQEFYVDYKPTNTTETSEMLLNGTGPCTYN  
KSGSRECEV

**Important features of the protein:****Signal peptide:**

amino acids 1-33

**Transmembrane domain:**

amino acids 420-442

**N-glycosylation sites.**

amino acids 126-129, 357-360, 496-499, 504-507

**cAMP- and cGMP-dependent protein kinase phosphorylation site.**

amino acids 465-468

**Tyrosine kinase phosphorylation site.**

amino acids 136-142

**N-myristoylation sites.**

amino acids 11-16, 33-38, 245-250, 332-337, 497-502, 507-512

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**FIGURE 125**

CCGTTATCGTCTTGCGCTACTGCTGA**AATG**TCCGTCCCGGAGGAGGAGGAGAGGCTTTTGCCGC  
TGACCCAGAGATGGCCCCGAGCGAGCAAATTCCTACTGTCCGGCTGCGCGGCTACCGTGGCCG  
AGCTAGCAACCTTTCCCTGGATCTCACAAAACTCGACTCCAAATGCAAGGAGAAGCAGCTC  
TTGCTCGGTTGGGAGACGGTGCAAGAGAATCTGCCCCCTATAGGGGAATGGTGCGCACAGCCC  
TAGGGATCATTGAAGAGGAAGGCTTTCTAAAGCTTTGGCAAGGAGTGACACCCGCCATTTACA  
GACACGTAGTGTATTCTGGAGGTCGAATGGTCACATATGAACATCTCCGAGAGGTTGTGTTTG  
GCAAAAGTGAAGATGAGCATTATCCCCTTTGGAAATCAGTCATTGGAGGGATGATGGCTGGTG  
TTATTGGCCAGTTTTTTAGCCAATCCAATGACCTAGTGAAGGTTTCAAGTGCAAATGGAAGGAA  
AAAGGAACTGGAAGGAAAACCATTCGATTTTCGTGGTGTACATCATGCATTTGCAAAAATCT  
TAGCTGAAGGAGGAATACGAGGGCTTTGGGCAGGCTGGGTACCCAATATACAAAGAGCAGCAC  
TGGTGAATATGGGAGATTTAACCACTTATGATACAGTGAAACACTACTTGGTATTGAATACAC  
CACTTGAGGACAATATCATGACTCACGGTTTATCAAGTTTATGTTCTGGACTGGTAGCTTCTA  
TTCTGGGAACACCAGCCGATGTCATCAAAGCAGAATAATGAATCAACCACGAGATAAACAAG  
GAAGGGGACTTTTGTATAAATCATCGACTGACTGCTTGATTCAAGGCTGTTCAAGGTGAAGGAT  
TCATGAGTCTATATAAAGGCTTTTTACCATCTTGGCTGAGAATGACCCCTTGGTCAATGGTGT  
TCTGGCTTACTTATGAAAAAATCAGAGAGATGAGTGGAGTCAGTCCATTT**TAA**

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**FIGURE 126**

MSVPEEEERLLPLTQRWPRÄSKFLLSGCAATVAELATFPLDLTKTRLQMQGEAALARLGDGAR  
ESAPYRGMVRTALGIIIEEGFLKLWQGVTPAIYRHVVYSGGRMVITYEHLREVVEFGKSEDEHYP  
LWKSIVIGMMAGVIGQFLANPTDLVKVQMOMEGKRKLEGKPLRFRGVHHAFAKILAEGGIRGL  
WAGWVPNIQRAALVNMGDLTTYDTVKHYLVNTPLEDNIMTHGLSSLCSGLVASILGTPADVI  
KSRIMNQPRDKQGRGLLYKSSTDCLIQAVQGEFMSLYKGFLPSWLRMTPWSMVFWLTYEKIR  
EMSGVSPF

**Transmembrane domains:**

amino acids 25-38, 130-147, 233-248



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**FIGURE 127**

CGCGGATCGGACCCAAGCAGGTCGGCGGGCGGCGGCAGGAGAGCGGCCGGGCGTCAGCTCCTCG  
ACCCCCGTGTGGGCTAGTCCAGCGAGGCGGACGGGCGGCGTGCGGCC**ATG**GCCAGGCCCGGC  
ATGGAGCGGTGGCGCGACCGGCTGGCGCTGGTGACGGGGGCGCTCGGGGGGCATCGGCGCGGCC  
GTGGCCCGGGCCCTGGTCCAGCAGGGACTGAAGGTGGTGGGCTGCGCCCGCACTGTGGGCAAC  
ATCGAGGAGCTGGCTGCTGAATGTAAGAGTGCAGGCTACCCCGGGACTTTGATCCCCTACAGA  
TGTGACCTATCAAATGAAGAGGACATCCTCTCCATGTTCTCAGCTATCCGTTCTCAGCACAGC  
GGTGTAGACATCTGCATCAACAATGCTGGCTTGGCCCGGCCTGACACCCTGCTCTCAGGCAGC  
ACCACTGGTTGGAAGGACATGTTCAATGTGAACGTGCTGGCCCTCAGCATCTGCACACGGGAA  
GCCTACCAGTCCATGAAGGAGCGGAATGTGGACGATGGGCACATCATTAACATCAATAGCATG  
TCTGGCCACCGAGTGTTACCCCTGTCTGTGACCCACTTCTATAGTGCCACCAAGTATGCCGTC  
ACTGCGCTGACAGAGGGACTGAGGCAAGAGCTTCGGGAGGCCAGACCCACATCCGAGCCACG  
TGCATCTCTCCAGGTGTGGTGGAGACACAATTGCGCTTCAAACCTCCACGACAAGGACCCTGAG  
AAGGCAGCTGCCACCTATGAGCAAATGAAGTGTCTCAAACCCGAGGATGTGGCCGAGGCTGTT  
ATCTACGTCCTCAGCACCCCGCACACATCCAGATTGGAGACATCCAGATGAGGCCACGGAG  
CAGGTGACCT**TAG**TGACTGTGGGAGCTCCTCCTTCCCTCCCCACCCTTCATGGCTTGCCTCCTG  
CCTCTGGATTTTAGGTGTTGATTTCTGGATCACGGGATACCACTTCCTGTCCACACCCCGACC  
AGGGGCTAGAAAATTTGTTTGAGATTTTATATCATCTTGTCAAATTGCTTCAGTTGTAAATG  
TGAAAAATGGGCTGGGGAAAGGAGGTGGTGTCCCTAATTGTTTTACTTGTTAACTTGTTCTTG  
TGCCCCTGGGCACTTGGCCTTTGTCTGCTCTCAGTGTCTTCCCTTTGACATGGGAAAGGAGTT  
GTGGCCAAAATCCCCATCTTCTTGACCTCAACGTCTGTGGCTCAGGGCTGGGGTGGCAGAGG  
GAGGCCTTACCTTATATCTGTGTTGTATCCAGGGCTCCAGACTTCCTCCTCTGCCCTGCCCC  
ACTGCACCCTCTCCCCCTTATCTATCTCCTTCTCGGCTCCCCAGCCAGTCTTGGCTTCTTGT  
CCCCTCCTGGGGTCATCCCTCCACTCTGACTCTGACTATGGCAGCAGAACACCAGGGCCTGGC  
CCAGTGGATTTTCATGGTGATCATTAAAAAAGAAAAATCGCAACCAAAAAAAAAAAAA

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**FIGURE 128**

MARPGMERWRDRLALVTGASGGIGAAVARALVQQGLKVVG CARTVGNIEELAAECKSAGYPGT  
LIPYRCDLSNEEDILSMFSAIRSQHSQVDICINNAGLARPD TLLSGSTSGWKDMFNVLALS  
ICTREAYQSMKERNVDDGHIININSMSGHRVLP LSVTHFY SATKYAVTALTEGLRQELREAQT  
HIRATCISPGVVETQFAFKLHDKDPEKAAATYEQMKCLKPEDVAEAVIYVLSTPAHIQIGDIQ  
MRPTEQVT

**Important features of the protein:****Signal peptide:**

amino acids 1-17

**N-myristoylation sites.**amino acids 18-24, 21-27, 22-28, 24-30, 40-46, 90-96, 109-115,  
199-205.**Short-chain alcohol dehydrogenase.**

amino acids 30-42, 104-114

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**FIGURE 129**

AACTTCTACATGGGCCTCCTGCTGCTGGTGCTCTTCCTCAGCCTCCTGCCGGTGGCCTACACC  
ATCATGTCCCTCCCACCCTCCTTTGACTGCGGGCCGTTTCAGGTGCAGAGTCTCAGTTGCCCCG  
GAGCACCTCCCCCTCCCGAGGCAGTCTGCTCAGAGGGCCTCGGCCCAGAATTCAGTTCTGGTT  
TCATGCCAGCCTGTAAAAGGCCATGGAACCTTGGGTGAATCACCGATGCCATTTAAGAGGGTT  
TTCTGCCAGGATGGAAATGTTAGGTCGTTCTGTGTCTGCGCTGTTCAATTCAGTAGCCACCAG  
CCACCTGTGGCCGTTGAGTGCTTGAAATTGAAGGAAGTGAAGAAATTAATTTCTCATGTATTTTT  
CTCATTTATTTATTAATTTTTTAAGTATAGTTGTACATATTTGGGGGTACATGTGATATTTGG  
ATACATGTATACAATATATAATGATCAAATCAGGGTAACTGGGATATCCATCACATCAAACAT  
TTATTTTTTTATTCCTTTTTAGACAGAGTCTCACTCTGTCAACCAGGCTGGAGTGCAGTGGTGCC  
ATCTCAGCTTACTGCAACCTCTGCCTGCCAGGTTCAAGCGATTCTCATGCCTCCACCTCCCAA  
GTAGCTGGGACTACAGGCATGCACCACAATGCCCAACTAATTTTTGTATTTTGTAGTAGAGACG  
GGGTTTTGCCATGTTGCCAGGCTGGCCTTGAACCTCCTGGCCTCAAACAATCCACTTGCCTCG  
GCCTCCCAAAGTGTTATGATTACAGGCGTGAGCCACCGTGCCTGGCCTAAACATTTATCTTTT  
CTTTGTGTTGGGAACCTTTGAAATTATACAATGAATTATTGTAACTGTCATCTCCCTGCTGTG  
CTATGGAACACTGGGACTTCTTCCCTCTATCTAACTGTATATTTGTACCAGTTAACCAACCGT  
ACTTCATCCCCACTCCTCTCTATCCTTCCCAACCTCTGATCACCTCATTCTACTCTCTACCTC  
CATGAGATCCACTTTTTTAGCTCCACATGTGAGTAAGAAAATGCAATATTTGTCTTTCTGTG  
CCTGGCTTATTTCACTTAACATAATGACTTCCTGTTCCATCCATGTTGCTGCAAATGACAGGA  
TTTCGTTCTTAATTTCAATTAATAAATAACCACACATGGCAAAA

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## **FIGURE 130**

MGLLLLVLFLSLLPVAYTIMSLPPSFDCGPFRCRVSVAREHLPSRGSLLRGPRPRI PVLVSCQ  
PVKGHGTLGESPMPEFKRVFCQDGNVRSFCVCAVHFSSHQPPVAVECLK

**Important features of the protein:**

**Signal peptide:**

amino acids 1-18

**N-myristoylation site.**

amino acids 86-92

**Zinc carboxypeptidases, zinc-binding region 2 signature.**

amino acids 68-79

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**FIGURE 131**

TTCTGAAGTAACGGAAGCTACCTTGTATAAAGACCTCAACACTGCTGACCATGATCAGCGCAG  
CCTGGAGCATCTTCCTCATCGGGACTAAAATTGGGCTGTTCCCTTCAAGTAGCACCTCTATCAG  
TTATGGCTAAATCCTGTCCATCTGTGTGTGCTGCGATGCGGGTTTCATTTACTGTAATGATC  
GCTTTCTGACATCCATTCCAACAGGAATACCAGAGGATGCTACAACCTCTCTACCTTCAGAACA  
ACCAAATAAATAATGCTGGGATTCCTTCAGATTTGAAAAACTTGCTGAAAGTAGAAAGAATAT  
ACCTATACCACAACAGTTTAGATGAATTTCTTACCAACCTCCCAAAGTATGTAAAAGAGTTAC  
ATTTGCAAGAAAATAACATAAGGACTATCACTTATGATTCACTTTTCAAAAATTCCCTATCTGG  
AAGAATTACATTTAGATGACAACCTCTGTCTCTGCAGTTAGCATAGAAGAGGGAGCATTCCGAG  
ACAGCAACTATCTCCGACTGCTTTTCTGTCCCGTAATCACCTTAGCACAAATTCCTGGGGTT  
TGCCCAGGACTATAGAAGAACTACGCTTGGATGATAATCGCATATCCACTATTTTCATCACCAT  
CTCTTCAAGGTCTCACTAGTCTAAAACGCCTGGTTCTAGATGGAAACCTGTTGAACAATCATG  
GTTTAGGTGACAAAGTTTTCTTCAACCTAGTTAATTTGACAGAGCTGTCCCTGGTGCGGAATT  
CCCTGACTGCTGCACCAGTAAACCTTCCAGGCACAAACCTGAGGAAGCTTTATCTTCAAGATA  
ACCACATCAATCGGGTGCCCCCAAATGCTTTTTCTTATCTAAGGCAGCTCTATCGACTGGATA  
TGTCCAATAATAACCTAAGTAATTTACCTCAGGGTATCTTTGATGATTTGGACAATATAACAC  
AACTGATTCTTCGCAACAATCCCTGGTATTGCGGGTGCAAGATGAAATGGGTACGTGACTGGT  
TACAATCACTACCTGTGAAGGTCAACGTGCGTGGGCTCATGTGCCAAGCCCCAGAAAAGGTTT  
GTGGGATGGCTATTAAGGATCTCAATGCAGAACTGTTTGATTGTAAGGACAGTGGGATTGTAA  
GCACCATTCAAGATAACCACTGCAATACCCAACACAGTGTATCCTGCCAAGGACAGTGGCCAG  
CTCCAGTGACCAAACAGCCAGATATTAAGAACCCCAAGCTCACTAAGGATCAACAAACCACAG  
GGAGTCCCTCAAGAAAAACAATTACAATTACTGTGAAGTCTGTACCTCTGATACCATTCTATA  
TCTCTTGAAACTTGCTCTACCTATGACTGCTTTGAGACTCAGCTGGCTTAACTGGGCCATA  
GCCCCGCATTTGGATCTATAACAGAAACAATTGTAACAGGGGAACGCAGTGAGTACTTGGTCA  
CAGCCCTGGAGCCTGATTCACCCTATAAAGTATGCATGGTTCCCATGGAAACCAGCAACCTCT  
ACCTATTTGATGAAACTCCTGTTTGTATTGAGACTGAAACTGCACCCCTTCGAATGTACAACC  
CTACAACCACCCTCAATCGAGAGCAAGAGAAAGAACCTTACAAAAACCCCAATTTACCTTTGG  
CTGCCATCATTGGTGGGGCTGTGGCCCTGGTTACCATTGCCCTTCTTGCTTTAGTGTGTTGGT  
ATGTTTCATAGGAATGGATCGCTCTTCTCAAGGAACTGTGCATATAGCAAAGGGAGGAGAAGAA  
AGGATGACTATGCAGAAGCTGGCACTAAGAAGGACAACCTCTATCCTGGAAATCAGGGAAACTT  
CTTTTCAGATGTTACCAATAAGCAATGAACCCATCTCGAAGGAGGAGTTTGTAAATACACACCA  
TATTTCTCTCTAATGGAATGAATCTGTACAAAAACAATCACAGTGAAAGCAGTAGTAACCGAA  
GCTACAGAGACAGTGGTATTCCAGACTCAGATCACTCACACTCATGATGCTGAAGGACTCACA  
GCAGACTTGTGTTTTGGGTTTTTTAAACCTAAGGGAGGTGATGGT

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**FIGURE 132**

MISAAWSIFLIGTKIGLFLQVAPLSVMAKSCPSVCRC DAGFIYCNDRELT SIPTGIPEDATTL  
YLQNNQINNAGIPSDLKNLLKVERIYLYHNSLDEFPTNL PKYVKELHLQENNIRTITYDSLK  
IPYLEELHLLDDNSVSAVSIEEGA FRDSNYLRLLFLSRNHLSTIPWGLPRTIEELRLDDNRIST  
ISSPSLQGLTSLKRLVLDGNLLNNHGLGDKVFFNLVNLTELSLVRNSLTAAPVNLPGTNLRKL  
YLQDNHINRVPPNAFSYLRQLYRLDMSNNLSNL PQGIFDDL DNITQLILRNNPWYCGCKMKW  
VRDWLQSLPVKVNVRGLMCQAPEKVRGMAIKDLNAELFDCKDSGIVSTIQITTAIPNTVYPAQ  
GQWPAPVTKQPDIKNPKLTKDQQTGSPSRKTITITVKS VTSDTIHISWKLALPMTALRLSWL  
KLGHSPAFGSITETIVTGERSEYLVTALEPDSPYKVCMPMETS NLYLFDETPVCIETETAPL  
RMYNP TTTLNREQEKEPYKNPNLPLAAIIGGAVALVTIALLALVCWYVHRNGSLFSRNCAYSK  
GRRRKDDYAEAGTKKDNSILEIRETSFQMLPISNEPISKEEFVIHTIFPPNGMNLYKNNHSES  
SSNRSYRDSGIPDS DSHS

**Important features of the protein:****Signal peptide:**

amino acids 1-28

**Transmembrane domain:**

amino acids 531-552

**N-glycosylation sites.**

amino acids 226-229, 282-285, 296-299, 555-558, 626-629, 633-636

**Tyrosine kinase phosphorylation site.**

amino acids 515-522

**N-myristoylation sites.**amino acids 12-17, 172-177, 208-213, 359-364, 534-539, 556-561,  
640-645**Amidation site.**

amino acids 567-570

**Leucine zipper pattern.**

amino acids 159-180

**Phospholipase A2 aspartic acid active site.**

amino acids 34-44

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**FIGURE 133**

CCGTCATCCCCCTGCAGCCACCCTTCCCAGAGTCCTTTGCCCAGGCCACCCCAGGCTTCTTG  
CAGCCCTGCCGGGCCACTTGTCTTCA**ATG**TCTGCCAGGGGGAGGTGGGAAGGAGGTGGGAGGAG  
GGCGTGCAGAGGCAGTCTGGGCTTGGCCAGAGCTCAGGGTGCTGAGCGTGTGACCAGCAGTGA  
GCAGAGGCCGGCCATGGCCAGCCTGGGGCTGCTGCTCCTGCTCTTACTGACAGCACTGCCACC  
GCTGTGGTCCCTCCTCACTGCCTGGGCTGGACACTGCTGAAAGTAAAGCCACCATTGCAGACCT  
GATCCTGTCTGCGCTGGAGAGAGCCACCGTCTTCCTAGAACAGAGGCTGCCTGAAATCAACCT  
GGATGGCATGGTGGGGGTCCGAGTGTGCTGGAAGAGCAGCTAAAAAGTGTCCGGGAGAAGTGGGC  
CCAGGAGCCCCCTGCTGCAGCCGCTGAGCCTGCGCGTGGGGATGCTGGGGGAGAAGCTGGAGGC  
TGCCATCCAGAGATCCCTCCACTACCTCAAGCTGAGTGATCCCAAGTACCTAAGAGAGTTCCA  
GCTGACCCTCCAGCCCCGGGTTTGGGAAGCTCCCACATGCCTGGATCCACACTGATGCCTCCTT  
GGTGTACCCACGTTCCGGGCCCCAGGACTCATTTCTCAGAGGAGAGAAGTGACGTGTGCCTGGT  
GCAGCTGCTGGGAACCGGGACGGACAGCAGCGAGCCCTGCGGCCTCTCAGACCTCTGCAGGAG  
CCTCATGACCAAGCCCGGCTGCTCAGGCTACTGCCTGTCCCACCAACTGCTCTTCTTCTCTG  
GGCCAGAATGAGGGGATGCACACAGGGACCACTCCAACAGAGCCAGGACTATATCAACCTCTT  
CTGCGCCAACATGATGGACTTGAACCGCAGAGCTGAGGCCATCGGATACGCCTACCCTACCCG  
GGACATCTTCATGGA<sup>1</sup>AAACATCATGTTCTGTGGAATGGGCGGCTTCTCCGACTTCTACAAGCT  
CCGGTGGCTGGAGGCCATTCTCAGCTGGCAGAAACAGCAGGAAGGATGCTTCGGGGAGCCTGA  
TGCTGAAGATGAAGAATTATCTAAAGCTATTCAATATCAGCAGCATTTTTTCGAGGAGAGTGAA  
GAGGCGAGAAAAACAATTTCCAGATTCTCGCTCTGTTGCTCAGGCTGGAGTACAGTGGCGCAA  
TCTCGGCTCACTGCAACCTTTGCCTCCTGGGTTCAAGCAATTCTCTTGCCTCATCCTCCCGAG  
TAGCTGGGACTACAGGAGCGTGCCACCATACTGGCTAATTTTTTATATTTTTTTTAGTAGAGAC  
AGGGTTTCATCATGTTGCTCATGCTGGTCTCGAACTCCTGATCTCAAGAGATCCGCCCACCTC  
AGGCTCCCAAAGTGTGGGATTAT**TAG**GTGTGAGCCACCGTGTCTGGCTGAAAAGCACTTTCAA  
GAGACTGTGTTGAATAAAGGGCCAAGGTTCTTGCCACCCAGCACTCATGGGGGCTCTCTCCCC  
TAGATGGCTGCTCCTCCCACAACACAGCCACAGCAGTGGCAGCCCTGGGTGGCTTCCTATACA  
TCCTGGCAGAATAACCCCCAGCAAACAGAGAGCCACACCCATCCACACCGCCACCACCAAGCA  
GCCGCTGAGACGGACGGTTCATGCCAGCTGCCTGGAGGAGGAACAGACCCCTTTAGTCCTCA  
TCCCTTAGATCCTGGAGGGCACGGATCACATCCTGGGAAGAAGGCATCTGGAGGATAAGCAAA  
GCCACCCCGACACCCAATCTTGAAGCCCTGAGTAGGCAGGGCCAGGGTAGGTGGGGGCCGGG  
AGGGACCCAGGTGTGAACGGATGAATAAAGTTCAACTGCAACTGAAAAAAAAA

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**FIGURE 134**

MSARGRWEGGRRACRGSGLARAQGAERVTSSEQRPAMASLGLLLLLLLLTALPPLWSSSLPG  
LDTAESKATIADLILSALERATVFLEQRLPEINLDGMVGVRVLEEQLKSVREKWAQEPLLQPL  
SLRVGMLGEKLEAAIQRSYLHYLKLSDPKYLREFQLTLQPGFWKLPHAWIHTDASLVYPTFGPQ  
DSFSEERSDVCLVQLLGTGTDSSSEPCGLSDLCRSLMTKPGCSGYCLSHQLLFFLWARMRGCTQ  
GPLQQSQDYINLFCANMMDLNRRAEAIGYAYPTRDIFMENIMFCGMGGFSDFYKLRWLEAILS  
WQKQQEGCFGEFPAEDEELSKAIQYQQHFSSRRVKRREKQFPDSRSVAQAGVQWRNLGSLQPLP  
PGFKQFSLILPSSWDYRSVPPYLANFYIFLVETGFHHVAHAGLELLISRDPPTSGSQSVGL

**Important features of the protein:****Signal peptide:**

amino acids 1-26

**Transmembrane domain:**

amino acids 39-56

**Tyrosine kinase phosphorylation sites.**

amino acids 149-156, 274-282

**N-myristoylation sites.**

amino acids 10-16, 20-26, 63-69, 208-214

**Amidation site.**

amino acids 10-14

**Glycoprotein hormones beta chain signature 1.**

amino acids 230-237



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**FIGURE 135**

GGTCTGAGTGCAGAGCTGCTGTCATGGCGGCCGCTCTGTGGGGCTTCTTTCCCGTCCTGCTGC  
TGCTGCTGCTATCGGGGGATGTCCAGAGCTCGGAGGTGCCCGGGGCTGCTGCTGAGGGATCGG  
GAGGGAGTGGGGTCCGCATAGGAGATCGCTTCAAGATTGAGGGGCGTGCAGTTGTTCCAGGGG  
TGAAGCCTCAGGACTGGATCTCGGCGGCCCGAGTGCTGGTAGACGGAGAAGAGCACGTCGGTT  
TCCTTAAGACAGATGGGAGTTTTGTGGTTCATGATATACCTTCTGGATCTTATGTAGTGGAAG  
TTGTATCTCCAGCTTACAGATTTGATCCCGTTTCGAGTGGATATCACTTCGAAAGGAAAAATGA  
GAGCAAGATATGTGAATTACATCAAAACATCAGAGGTTGTCAGACTGCCCTATCCTCTCCAAA  
TGAAATCTTCAGGTCCACCTTCTTACTTTATTAAAAGGGAATCGTGGGGCTGGACAGACTTTC  
TAATGAACCCAATGGTTATGATGATGGTTCTTCCTTTATTGATATTTGTGCTTCTGCCTAAAG  
TGGTCAACACAAGTGATCCTGACATGAGACGGGAAATGGAGCAGTCAATGAATATGCTGAATT  
CCAACCATGAGTTGCCTGATGTTTCTGAGTTCATGACAAGACTCTTCTCTTCAAAATCATCTG  
GCAAATCTAGCAGCGGCAGCAGTAAACAGGCAAAAGTGGGGCTGGCAAAGGAGGTAGTCAG  
GCCGTCCAGAGCTGGCATTTCACACAAACACGGCAACACTGGGTGGCATCCAAGTCTTGAAAA  
CCGTGTGAAGCAACTACTATAAACTTGAGTCATCCCGACGTTGATCTCTTACAACGTGTATGTT  
AACTTTTTAGCACATGTTTTGTACTTGGTACACGAGAAAACCCAGCTTTCATCTTTTGTCTGT  
ATGAGGTCAATATTGATGTCACTGAATTAATTACAGTGTCTTATAGAAAATGCCATTAATAAA  
TTATATGAACTACTATACATTATGTATATTAATTAACATCTTAATCCAGAAATCAAAAAAA  
AAAAAAAAAAAAAAAAAAAAA

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**FIGURE 136**

MAAALWGFFPVLLLLLLSGDVQSSEVPGAAAEAGSGSGVGIGDRFKIEGRAVVPGVKPQDWIS  
AARVLVDGEEHVGFLLKTDGSFVVHDIPSGSYVVEVVS PAYRFDPVRVDITSKGKMRARYVNYI  
KTSEVVRLPYPLQMKSSGPPSYFIKRESWGWTDFLMNPMVMMMLVLLIFVLLPKVVNTSDPD  
MRREMEQSMNMLNSNHELDPDVSEFMTRLFSSKSSGKSSSGSSKTGKSGAGKRR

**Important features of the protein:****Signal sequence:**

amino acids 1-23

**Transmembrane domain:**

amino acids 161-182

**N-glycosylation site.**

amino acids 184-187

**Glycosaminoglycan attachment sites.**

amino acids 37-40, 236-239

**cAMP- and cGMP-dependent protein kinase phosphorylation site.**

amino acids 151-154

**N-myristoylation sites.**

amino acids 33-38, 36-41, 38-44, 229-234

**Amidation site.**

amino acids 238-241

**ATP/GTP-binding site motif A (P-loop).**

amino acids 229-236

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**FIGURE 137**

GATGGCGCAGCCACAGCTTCTGTGAGATTTCGATTTCTCCCCAGTTCCCCTGTGGGTCTGAGGG  
GACCAGAAGGGTGAGCTACGTTGGCTTTCTGGAAGGGGAGGCTATATGCGTCAATTCCCCAAA  
ACAAGTTTTGACATTTCCCCTGAAATGTCATTCTCTATCTATTCACTGCAAGTGCCTGCTGTT  
CCAGGCCTTACCTGCTGGGCACCTAACGGCGGAGCCAGGATGGGGACAGAATAAAGGAGCCACG  
ACCTGTGCCACCAACTCGCACTCAGACTCTGAACTCAGACCTGAAATCTTCTCTTCACGGGAG  
GCTTGGCAGTTTTTCTTACTCCTGTGGTCTCCAGATTTTCAGGCCTAAGATGAAAGCCTCTAGT  
CTTGCCCTCAGCCTTCTCTCTGCTGCGTTTTATCTCCTATGGACTCCTTCCACTGGACTGAAG  
ACACTCAATTTGGGAAGCTGTGTGATCGCCACAAACCTTCAGGAAATACGAAATGGATTTTCT  
GAGATACGGGGCAGTGTGCAAGCCAAAGATGGAAACATTGACATCAGAATCTTAAGGAGGACT  
GAGTCTTTGCAAGACACAAAGCCTGCGAATCGATGCTGCCTCCTGCGCCATTTGCTAAGACTC  
TATCTGGACAGGGTATTTAAAACTACCAGACCCCTGACCATTATACTCTCCGGAAGATCAGC  
AGCCTCGCCAATTCTTTCTTACCATCAAGAAGGACCTCCGGCTCTCTCATGCCACATGACA  
TGCCATTGTGGGGAGGAAGCAATGAAGAAATACAGCCAGATTCTGAGTCACTTTGAAAAGCTG  
GAACCTCAGGCAGCAGTTGTGAAGGCTTTGGGGGAAGTAGACATTCTTCTGCAATGGATGGAG  
GAGACAGAATAGGAGGAAAGTGATGCTGCTGCTAAGAATATTCGAGGTCAAGAGCTCCAGTCT  
TCAATACCTGCAGAGGAGGCATGACCCCAAACCACCATCTCTTTACTGTACTAGTCTTGTGCT  
GGTCACAGTGTATCTTATTTATGCATTACTTGCTTCCTTGCAATGATTGTCTTTATGCATCCCC  
AATCTTAATTGAGACCATACTTGTATAAGATTTTTGTAAATATCTTTCTGCTATTGGATATATT  
TATTAGTTAATATATTTATTTATTTTTTGCTATTTAATGTATTTATTTTTTACTTGGACATG  
AAACTTTAAAAAAATTCACAGATTATATTTATAACCTGACTAGAGCAGGTGATGTATTTTAT  
ACAGTAAAAAATAACCTTGTAATTCCTAGAAGAGTGGCTAGGGGGTTATTCAATTTGTAT  
TCAACTAAGGACATATTTACTCATGCTGATGCTCTGTGAGATATTTGAAATTGAACCAATGAC  
TACTTAGGATGGGTGTGGAATAAGTTTTGATGTGGAATTGCACATCTACCTTACAATTACTG  
ACCATCCCCAGTAGACTCCCCAGTCCCATTAATTGTGTATCTTCCAGCCAGGAATCCTACACGG  
CCAGCATGTATTTCTACAAATAAAGTTTTCTTTGCATACCAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 138**

MRQFPKTSFDISPEMSFSIYSLQVPAVPGITCWALTAEPGWGQNGATTTCATNSHSDSELRPE  
IFSSREAWQFFLLWSPDFRPKMKASSLAFLSLLSAAFYLLWTPSTGLKTLNLGSCVIATNLQE  
IRNGFSEIRGSVQAKDGNIDIRILRRTESLQDTKPANRCCLLRHLLRLYLDRVFKNYQTPDHY  
TLRKISSLANSFLTIIKKDLRLSHAHMTCHCGEEAMKKYSQILSHFEKLEPQAAVVKALGELDI  
LLQWMEETE

**Important features of the protein:**

**Signal peptide:**

amino acids 1-42

**cAMP- and cGMP-dependent protein kinase phosphorylation sites.**

amino acids 192-195, 225-228

**N-myristoylation sites.**

amino acids 42-47, 46-51, 136-141

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**FIGURE 139**

CCTGGAGCCGGAAGCGCGGCTGCAGCAGGGCGAGGCTCCAGGTGGGGTCGGTTCCGCATCCAG  
CCTAGCGTGTCCACG**ATG**CGGCTGGGCTCCGGGACTTTCGCTACCTGTTGCGTAGCGATCGAG  
GTGCTAGGGATCGCGGTCTTCCTTCGGGGATTCTTCCCGGCTCCCGTTCGTTCTCTGCCAGA  
GCGGAACACGGAGCGGAGCCCCAGCGCCCGAACCTCGGCTGGAGCCAGTTCTAACTGGACC  
ACGCTGCCACCACCTCTCTTCAGTAAAGTTGTTATTGTTCTGATAGATGCCTTGAGAGATGAT  
TTTGTGTTTGGGTCAAAGGGTGTGAAATTTATGCCCTACACAACTTACCTTGTGGAAAAAGGA  
GCATCTCACAGTTTTTGTGGCTGAAGCAAAGCCACCTACAGTTACTATGCCTCGAATCAAGGCA  
TTGATGACGGGGAGCCTTCCTGGCTTTGTGACGTCATCAGGAACCTCAATTCTCCTGCACTG  
CTGGAAGACAGTGTGATAAGACAAGCAAAAGCAGCTGGAAAAAGAATAGTCTTTTATGGAGAT  
GAAACCTGGGTAAATTATTCCCAAAGCATTTTGTGGAATATGATGGAACAACCTCATTTTTTC  
GTGTCAGATTACACAGAGGTGGATAATAATGTCACGAGGCATTTGGATAAAGTATTA AAAAGA  
GGAGATTGGGACATATTAATCCTCCACTACCTGGGGCTGGACCACATTGGCCACATTTTCAGGG  
CCCAACAGCCCCCTGATTGGGCAGAAGCTGAGCGAGATGGACAGCGTGCTGATGAAGATCCAC  
ACCTCACTGCAGTCGAAGGAGAGAGAGACGCCTTTACCCAAATTGCTGGTTCTTTGTGGTGAC  
CATGGCATGTCTGAAACAGGAAGTCACGGGGCCTCCTCCACCGAGGAGGTGAATACACCTCTG  
ATTTTAATCAGTTCGTGCTTTGAAAGGAAACCGGTGATATCCGACATCCAAAGCACGTCCAA  
**TAG**ACGGATGTGGCTGCGACACTGGCGATAGCACTTGGCTTACCGATTCCAAAAGACAGTGTA  
GGGAGCCTCCTATTCCCAAGTTGTGGAAGGAAGACCAATGAGAGAGCAGTTGAGATTTTTTACAT  
TTGAATACAGTGCAGCTTAGTAACTGTTGCAAGAGAATGTGCCGTGATATGAAAAAGATCCT  
GGGTTTGAGCAGTTTAAATGTCAGAAAGATTGCATGGGAACTGGATCAGACTGTACTTGGAG  
GAAAAGCATTGAGAAGTCTATTCAACCTGGGCTCCAAGGTTCTCAGGCAGTACCTGGATGCT  
CTGAAGACGCTGAGCTTGTCCCTGAGTGCACAAGTGGCCAGTTCTCACCTGCTCCTGCTCA  
CGGTCCCACAGGCACTGCACAGAAAGGCTGAGCTGGAAGTCCCACTGTCATCTCCTGGGTTTT  
CTCTGCTCTTTTATTTGGTGATCCTGGTTCTTTCGGCCGTTACGTCATTGTGTGCACCTCAG  
CTGAAAGTTTCGTGCTACTTCTGTGGCCTCTCGTGGCTGGCGGCAGGCTGCCTTTCGTTTACCA  
GACTCTGGTTGAACACCTGGTGTGTGCCAAGTGCTGGCAGTGCCCTGGACAGGGGGCCTCAGG  
GAAGGACGTGGAGCAGCCTTATCCCAGGCCTCTGGGTGTCCCGACACAGGTGTTACATCTGT  
GCTGTCAGGTCAGATGCCTCAGTTCTTGGAAAGCTAGGTTCTGCGACTGTTACCAAGGTGAT  
TGTAAGAGCTGGCGGTACAGAGGAACAAGCCCCCAGCTGAGGGGGTGTGTGAATCGGACA  
GCCTCCCAGCAGAGGTGTGGGAGCTGCAGCTGAGGGAAGAAGAGACAATCGGCCTGGACACTC  
AGGAGGGTCAAAGGAGACTTGGTCGCACCACTCATCCTGCCACCCCAGAATGCATCCTGCC  
TCATCAGGTCCAGATTTCTTTCCAAGGCGGACGTTTCTGTTGGAATTCTTAGTCCTTGGCCT  
CGGACACCTTCATTTCGTTAGCTGGGGAGTGGTGGTGAGGCAGTGAAGAAGAGGCGGATGGTCA  
CACTCAGATCCACAGAGCCCAGGATCAAGGGACCCACTGCAGTGGCAGCAGGACTGTTGGGCC  
CCCACCCCAACCTGCACAGCCCTCATCCCCTCTGGCTTGAGCCGTCAGAGGCCCTGTGCTG  
AGTGTCTGACCGAGACACTCACAGCTTTGTATCAGGGCACAGGCTTCCTCGGAGCCAGGATG  
ATCTGTGCCACGCTTGACCTCGGGCCCATCTGGGCTCATGCTCTCTCTCCTGCTATTGAATT  
AGTACCTAGCTGCACACAGTATGTAGTTACCAAAGAATAAACGGCAATAATTGAGAAAAAAA

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**FIGURE 140**

MRLGSGTFATCCVAIEVLGIÁVFLRGFFPAPVRSSARAEGAEPPAPEPSAGASSNWTTLPPP  
LFSKVIVIVLIDALRDDFVFGSKGVKFMPTTYLVEKGASHSFVAEAKPPTVTMPRIKALMTGS  
LPGFVDVIRNLNSPALLEDVIRQAKAAGKRIVFYGDETWVKLFPKHFVEYDGTTSFFVSDYT  
EVDNNVTRHLDKVLKRGDWDILILHYLGLDGHIGHISGPN SPLIGQKLSEMDSVLMKIHTSLQS  
KERETPLPNLLVLCGDHGMSETGSHGASSTEEVNTPLILISSAFERKPGDIRHPKHVQ

**Important features of the protein:****Signal peptide:**

amino acids 1-34

**Transmembrane domain:**

amino acids 58-76

**N-glycosylation sites.**

amino acids 56-60, 194-198

**N-myristoylation sites.**amino acids 6-12, 52-58, 100-106, 125-131, 233-239, 270-276,  
275-281, 278-284**Amidation site.**

amino acids 154-158

**Cell attachment sequence.**

amino acids 205-208

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**FIGURE 141**

GGCACGAGGCAAGCCTTCCAGGTTATCGTGACGCACCTTGAAAGTCTGAGAGCTACTGCCCTA  
CAGAAAGTTACTAGTGCCCTAAAGCTGGCGCTGGCACTG**ATG**TTACTGCTGCTGTTGGAGTAC  
AACTTCCCTATAGAAAACAACCTGCCAGCACCTTAAGACCACTCACACCTTCAGAGTGAAGAAC  
TTAAACCCGAAGAAATTCAGCATTTCATGACCAGGATCACAAAGTACTGGTCCTGGACTCTGGG  
AATCTCATAGCAGTTCCAGATAAAAACTACATACGCCCAGAGATCTTCTTTGCATTAGCCTCA  
TCCTTGAGCTCAGCCTCTGCGGAGAAAGGAAGTCCGATTCTCCTGGGGGTCTCTAAAGGGGAG  
TTTTGTCTCTACTGTGACAAGGATAAAGGACAAAGTCATCCATCCCTTCAGCTGAAGAAGGAG  
AAACTGATGAAGCTGGCTGCCCCAAAAGGAATCAGCACGCCGGCCCTTCATCTTTTATAGGGCT  
CAGGTGGGCTCCTGGAACATGCTGGAGTCGGCGGCTCACCCCGGATGGTTCATCTGCACCTCC  
TGCAATTGTAATGAGCCTGTTGGGGTGACAGATAAATTTGAGAACAGGAAACACATTGAATTT  
TCATTTCAACCAGTTTGCAAAGCTGAAATGAGCCCCAGTGAGGTCAGCGAT**TAG**GAAACTGCC  
CCATTGAACGCCTTCCTCGCTAATTTGAACTAATTGTATAAAAACACCAAACCTGCTCACT

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**FIGURE 142**

MLLLLLLEYNFPIENNCQHLKTTHTFRVKNLNPKKFSIHDQDHKVLVLDSGNLIAVPDKNYIRP  
EIFFALASSLSSASAEKGSPIILGVSKGEFCLYCDKDKGQSHPSLQLKKEKLMKLAAQKESAR  
RPFIFYRAQVGSWNMLESAAHPGWFICTSCNCNEPVGVTDKFENRKHIEFSFQPVCKAEMSPS  
EVSD

**cAMP- and cGMP-dependent protein kinase phosphorylation site.**  
amino acids 33-36

**N-myristoylation site.**  
amino acids 50-55, 87-92

**Interleukin-1**  
amino acids 37-182





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## **FIGURE 144**

MLGLPWKGGLSWALLLLLLLGSQILLIYAWHFHEQRDCDEHNVMARYLPATVEFAVHTFNQQSK  
DYYAYRLGHILNSWKEQVESKTVFSMELLGLRTRCGKFEDDIDNCHFQESTELNNTFTCFFTI  
STRPWMTQFSLLNKTCLEGFH

**Important features of the protein:**

**Signal peptide:**

amino acids 1-25

**N-glycosylation sites.**

amino acids 117-121, 139-143

**N-myristoylation site.**

amino acids 9-15

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**FIGURE 145**

CTGTGCAGCTCGAGGCTCCAGAGGCACACTCCAGAGAGAGCCAAGGTTCTGACGCGATGAGGA  
AGCACCTGAGCTGGTGGTGGCTGGCCACTGTCTGCATGCTGCTCTTCAGCCACCTCTCTGCGG  
TCCAGACGAGGGGCATCAAGCACAGAATCAAGTGGAACCGGAAGGCCCTGCCCAGCACTGCCC  
AGATCACTGAGGCCCAGGTGGCTGAGAACCGCCCGGGAGCCTTCATCAAGCAAGGCCGCAAGC  
TCGACATTGACTTCGGAGCCGAGGGCAACAGGTACTACGAGGCCAACTACTGGCAGTTCCCCG  
ATGGCATCCACTACAACGGCTGCTCTGAGGCTAATGTGACCAAGGAGGCATTTGTCACCGGCT  
GCATCAATGCCACCCAGGCGGCGAACCAGGGGGAGTTCCAGAAGCCAGACAACAAGCTCCACC  
AGCAGGTGCTCTGGCGGCTGGTCCAGGAGCTCTGCTCCCTCAAGCATTGCGAGTTTTGGTTGG  
AGAGGGGCGCAGGACTTCGGGTCAACATGCACCAGCCAGTGCTCCTCTGCCTTCTGGCTTTGA  
TCTGGCTCATGGTGAAATTAAGCTTGCCAGGAGGCTGGCAGTACAGAGCGCAGCAGCGAGCAAA  
TCCTGGCAAGTGACCCAGCTCTTCTCCCCCAAACCCACGCGTGTTCTGAAGGTGCCCAGGAGC  
GGCGATGCACTCGCACTGCAAATGCCGCTCCACGTATGCGCCCTGGTATGTGCCTGCGTTCT  
GATAGATGGGGGACTGTGGCTTCTCCGTCACTCCATTCTCAGCCCCTAGCAGAGCGTCTGGCA  
CACTAGATTAGTAGTAAATGCTTGATGAGAAGAACACATCAGGCACTGCGCCACCTGCTTCAC  
AGTACTTCCCAACAACCTCTTAGAGGTAGGTGTATTCCCGTTTTACAGATAAGGAACTGAGGC  
CCAGAGAGCTGAAGTACTGCACCCAGCATCACCAGCTAGAAAGTGGCAGAGCCAGGATTCAAC  
CCTGGCTTGTCTAACCCAGGTTTTCTGCTCTGTCCAATTCCAGAGCTGTCTGGTGATCACTT  
TATGTCTCACAGGGACCCACATCCAACATGTATCTCTAATGAAATTGTGAAAGCTCCATGTT  
TAGAAATAAATGAAAACACCTGA

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## **FIGURE 146**

MRKHLSSWWLATVCMLLFSHL SAVQTRGIKHKRKNRKALPSTAQITEAQVAENRPGAFIKQG  
RKLDIDFGAEGNRYYEANYWQFPDGIHYNGCSEANVTKEAFVTGCINATQAANQGEFQKPDNK  
LHQQVLWRLVQELCSLKHCEFWLERGAGLRVTMHQPVLLCLLALIWLMVK

**Important features of the protein:**

**Signal peptide:**

amino acids 1-26

**Transmembrane domain:**

amino acids 157-171

**N-glycosylation sites.**

amino acids 98-102, 110-114

**Tyrosine kinase phosphorylation site.**

amino acids 76-83

**N-myristoylation sites.**

amino acids 71-77, 88-94, 93-99, 107-113, 154-160

**Amidation site.**

amino acids 62-66

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**FIGURE 147**

GCCTTGGCCTCCCAAAGGGCTGGGATTATAGGCGTGACCACCATGTCTGGTCCAGAGTCTCAT  
TTCCTGATGATTTATAGACTCAAAGAAAACTATGTTCAGAAGCTCTCTTCTCTTCTGGCCTC  
CTCTCTGTCTTCTTTCCCTCTTTCTTCTTATTTTAATTAGTAGCATCTACTCAGAGTCATGCA  
AGCTGGAAATCTTTCATTTTGCTTGTCAGTGGGGTAGGTCAGTCTTAGTTTTATTTTT  
TGAAATTTCAACTTTCAGATTCAGGGGGTACATGTGAAGGTTTGTTTTATGAGTATATTGCAT  
GATGCTGAGGTTTGGGGT

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## **FIGURE 148**

MFRSSLLFWPPLCLLSLFLILISSIYSESKLEIFHFACQWGRSLSLSFYFLKFQLSDSGGT  
CEGLFYEYIA

**Important features of the protein:**

**Signal peptide:**

amino acids 1-25

**N-myristoylation site.**

amino acids 62-68

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**FIGURE 149**

GTCTCCGCGTCACAGGAAC TTCAGCACCCACAGGGCGGACAGCGCTCCCCTCTACCTGGAGAC  
TTGACTCCCGCGCGCCCCAACCCCTGCTTATCCCTTGACCGTCGAGTGTGAGAGATCCTGCAGC  
CGCCAGTCCCGGGCCCCCTCTCCCGCCCCACACCCACCCCTCCTGGCTCTTCCTGTTTTACTCC  
TCCTTTTCATTCATAACAAAAGCTACAGCTCCAGGAGCCCAGCGCCGGGCTGTGACCCAAGCC  
GAGCGTGGAAGAATG GGGGTTTCCTCGGGACCGGCACTTGATTCTGGTGTTAGTGCTCCCGATT  
CAAGCTTTCCCCAACCTGGAGGAAGCCAAGACAAATCTCTACATAATAGAGAATTAAGTGCA  
GAAAGACCTTTGAATGAACAGATTGCTGAAGCAGAAGAAGACAAGATTAAAAAACATATCCT  
CCAGAAAACAAGCCAGGTGAGAGCAACTATTCTTTTGTTGATAACTTGAACTGCTAAAGGCA  
ATAACAGAAAAGGAAAAAATTGAGAAAGAAAGACAATCTATAAGAAGCTCCCCACTTGATAAT  
AAGTTGAATGTGGAAGATGTTGATTCAACCAAGAATCGAAAAC TGATCGATGATTATGACTCT  
ACTAAGAGTGGATTGGATCATAAATTTCAAGATGATCCAGATGGTCTTCATCAACTAGACGGG  
ACTCCTTTAACCGCTGAAGACATTGTCCATAAAATCGCTGCCAGGATTTATGAAGAAAATGAC  
AGAGCCGTGTTTGACAAGATTGTTTCTAACTACTTAATCTCGGCCTTATCACAGAAAGCCAA  
GCACATACACTGGAAGATGAAGTAGCAGAGGTTTTACAAAAATTAATCTCAAAGGAAGCCAAC  
AATTATGAGGAGGATCCCAATAAGCCCACAAGCTGGACTGAGAATCAGGCTGGAAAAATACCA  
GAGAAAGTGACTCCAATGGCAGCAATTCAAGATGGTCTTGCTAAGGGAGAAAACGATGAAACA  
GTATCTAACACATTAACCTTGACAAATGGCTTGGAAGGAGAACTAAAACCTACAGTGAAGAC  
AACTTTGAGGAACTCCAATATTTCCCAAATTTCTATGCGCTACTGAAAAGTATTGATTGAGAA  
AAAGAAGCAAAAGAGAAAGAAACACTGATTACTATCATGAAAACACTGATTGACTTTGTGAAG  
ATGATGGTGAAATATGGAACAATATCTCCAGAAGAAGGTGTTTCCTACCTTGAAAACCTGGAT  
GAAATGATTGCTCTTCAGACCAAAAACAAGCTAGAAAAAAATGCTACTGACAATATAAGCAAG  
CTTTTCCCAGCACCATCAGAGAAGAGTCATGAAGAAACAGACAGTACCAAGGAAGAAGCAGCT  
AAGATGGAAAAGGAATATGGAAGCTTGAAAGGATCCACAAAAGATGATAACTCCAACCCAGGA  
GGAAAGACAGATGAACCCAAAGGAAAAACAGAAGCCTATTTGGAAGCCATCAGAAAAAATATT  
GAATGGTTGAAGAAACATGACAAAAAGGGAAATAAAGAAGATTATGACCTTTCAAAGATGAGA  
GACTTCATCAATAAACAAGCTGATGCTTATGTGGAGAAAGGCATCCTTGACAAGGAAGAAGCC  
GAGGCCATCAAGCGCATTTATAGCAGCCTGTAA AAAATGGCAAAAGATCCAGGAGTCTTCAAC  
TGTTTCAGAAAACATAATATAGCTTAAAACACTTCTAATTCTGTGATTAAATTTTTTGACCC  
AAGGGTTATTAGAAAGTGCTGAATTTACAGTAGTTAACCTTTTACAAGTGGTTAAAACATAGC  
TTTCTTCCCGTAAAAACTATCTGAAAGTAAAGTTGTATGTAAGCTGAAAAAAAAAAAAAAAAA  
AAA

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**FIGURE 150**

MGFLGTGTWILVLVLPIQAFPKPGGSQDKSLHNRELSAERPLNEQIAEAEEDKIKKTYPPENK  
PGQSNYSFVDNLNLLKAITEKEKIEKERQSIRSSPLDNKLNVEDVDSTKNRKLIDDYDSTKSG  
LDHKFQDDPDGLHQLDGTPLTAEDIVHKIAARIYEENDRAVFDKIVSKLLNLGLITESQAHTL  
EDEVAEVLQKLISKEANNYEEDPNKPTSWTENQAGKIPEKVTMAAIQDGLAKGENDETVSNT  
LTLTNGLERRTKTYSEDNFEELQYFPNFIYALLKSIDSEKEAKEKETLITIMKTLIDFVKMMVK  
YGTISPEEGVSYLENLDEMIALQTKNKLEKNATDNISKLFAPSEKSHEETDSTKEEAAKMEK  
EYGLKDKSTKDDNSNPGGKTDEPKGKTEAYLEAIRKNIEWLKKHDKKGNKEDYDLSKMRDFIN  
KQADAYVEKGILDKEEAETKRIYSSL

**N-glycosylation sites:**

amino acids 68-71, 346-349, 350-353

**Casein kinase II phosphorylation site:**

amino acids 70-73, 82-85, 97-100, 125-128, 147-150, 188-191, 217-  
220, 265-268, 289-292, 305-308, 320-323, 326-329, 362-365, 368-  
341, 369-372, 382-385, 386-389, 387-390

**N-myristoylation sites:**

amino acids 143-148, 239-244



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**FIGURE 151**

CGGCTCGAGGCTCCCGCCAGGAGAAAGGAACATTCTGAGGGGAGTCTACACCCTGTGGAGCTC  
AAG**ATG**TCCTGAGTGGGGCGCTGTGCTTCCGAATGAAGGACTCGGCATTGAAGGTGCTTTAT  
CTGCATAATAACCAGCTTCTAGCTGGAGGGCTGCATGCAGGGAAGGTCATTAAAGGTGAAGAG  
ATCAGCGTGGTCCCCAATCGGTGGCTGGATGCCAGCCTGTCCCCCGTCATCCTGGGTGTCCAG  
GGTGAAGCCAGTGCCTGTGATGTGGGGTGGGGCAGGAGCCGACTCTAACACTAGAGCCAGTG  
AACATCATGGAGCTCTATCTTGGTGCCAAGGAATCCAAGAGCTTCACCTTCTACCGGCGGGAC  
ATGGGGCTCACCTCCAGCTTCGAGTCGGCTGCCACCCGGGCTGGTTCCTGTGCACGGTGCCT  
GAAGCCGATCAGCCTGTGAGCTCACCCAGCTTCCCGAGAATGGTGGCTGGAATGCCCCCATC  
ACAGACTTCTACTTCCAGCAGTGTGACT**TAG**GGCAACGTGCCCCCAGAACTCCCTGGGCAGAG  
CCAGCTCGGGTGAGGGGTGAGTGGAGGAGACCCATGGCGGACAATCACTCTCTGCTCTCAG  
GACCCCCACGTCTGACTTAGTGGGCACCTGACCACCTTGTCTTCTGGTTCACAGTTTGGATAA  
ATTCTGAGATTTGGAGCTCAGTCCACGGTCTCCCCCACTGGATGGTGCTACTGCTGTGGAAC  
CTTGTA AAAACCATGTGGGGTAAACTGGGAATAACATGAAAAGATTTCTGTGGGGGTGGGGTG  
GGGGAGTGGTGGGAATCATTCCTGCTTAATGGTAAGTGTACCCCTGAGCCCCGAG  
GCCAACCCATCCCCAGTTGAGCCTTATAGGGTCAGTAGCTCTCCACATGAAGTCCTGTCACTC  
ACCACTGTGCAGGAGAGGGAGGTGGTCATAGAGTCAGGGATCTATGGCCCTTGGCCCAGCCCC  
ACCCCTTCCCTTTAATCCTGCCACTGTGATATGCTACCTTTCTATCTCTTCCCTCATCATC  
TTGTTGTGGGCATGAGGAGGTGGTGATGTCAGAAGAAATGGCTCGAGCTCAGAAGATAAAAGA  
TAAGTAGGGTATGCTGATCCTCTTTTAAAAACCAAGATACAATCAAATCCCAGATGCTGGT  
CTCTATTCCCATGAAAAAGTGCTCATGACATATTGAGAAGACCTACTTACAAAGTGGCATATA  
TTGCAATTTATTTAATTAAAAGATACCTATTTATATATTTCTTTATAGAAAAAGTCTGGAA  
GAGTTTACTTCAATTGTAGCAATGTGAGGGTGGTGGCAGTATAGGTGATTTTTCTTTAATTC  
TGTTAATTTATCTGTATTTCCCTAATTTTCTACAATGAAGATGAATTCCTTGATATAAAAATAA  
GAAAAGAAATTAATCTTGAGGTAAGCAGAGCAGACATCATCTCTGATTGTCTCAGCCTCCAC  
TTCCCCAGAGTAAATTCAAATTGAATCGAGCTCTGCTGCTGCTGGTTGGTTGTAGTAGTCA  
GGAAACAGATCTCAGCAAAGCCACTGAGGAGGAGGCTGTGCTGAGTTTGTGTGGCTGGAATCT  
CTGGGTAAAGAACTTAAAGAACA AAAATCATCTGGTAATTCTTTCTAGAGGATCACAGCCC  
CTGGGATTCCAAGGCATTGGATCCAGTCTCTAAGAAGGCTGCTGTACTGGTTGAATTGTGTCC  
CCCTCAAATTCACATCCTTCTTGGAATCTCAGTCTGTGAGTTTATTTGGAGATAAGGTCTCTG  
CAGATGTAGTTAGTTAAGACAAGGTCATGCTGGATGAAGGTAGACCTAAATTCAATATGACTG  
GTTTCTTGTATGAAAAGGAGAGGACACAGAGACAGAGGAGACGCGGGGAAGACTATGTAAAG  
ATGAAGGCAGAGATCGGAGTTTTGCAGCCACAAGCTAAGAAACACCAAGGATTGTGGCAACCA  
TCAGAAGCTTGGAAGAGGCAAAGAAGAATTCTTCCCTAGAGGCTTTAGAGGGATAACGGCTCT  
GCTGAAACCTTAATCTCAGACTTCCAGCCTCCTGAACGAAGAAAGAATAAATTTTCGGCTGTTT  
TAAGCCACCAAGGATAATTGGTTACAGCAGCTCTAGGAACTAATACAGCTGCTAAAATGATC  
CCTGTCTCCTCGTGTTTACATTCTGTGTGTGTCCCTCCCACAATGTACCAAAGTTGTCTTTG  
TGACCAATAGAATATGGCAGAAGTGATGGCATGCCACTTCCAAGATTAGGTTATAAAAGACAC  
TGCAGCTTCTACTTGAGCCCTCTCTCTCTGCCACCCACCGCCCCCAATCTATCTTGGCTCACT  
CGCTCTGGGGGAAGCTAGCTGCCATGCTATGAGCAGGCCTATAAAGAGACTTACGTGGTAAAA  
AATGAAGTCTCCTGCCCCACAGCCACATTAGTGAACCTAGAAGCAGAGACTCTGTGAGATAATC  
GATGTTTGTGTTTAAAGTTGCTCAGTTTTGGTCTAACTTGTTATGCAGCAATAGATAAATAA  
TATGCAGAGAAAGAG

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## **FIGURE 152**

MVLSGALCFRMKDSALKVLYLHNNQLLAGGLHAGKVIKGEESVVPNRWLDASLSPVILGVQG  
GSQCLSCGVGQEPTLTLEPVNIMELYLGAKESKSFTFYRRDMGLTSSFESAAYPGWFLCTVPE  
ADQPVRLTQLPENGGWNAPITDFYFQQCD

### **N-myristoylation sites.**

amino acids 29-34, 30-35, 60-65, 63-68, 73-78, 91-96, 106-111

### **Interleukin-1 signature.**

amino acids 111-131

### **Interleukin-1 proteins.**

amino acids 8-29, 83-120, 95-134, 64-103

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**FIGURE 153**

CTTCAGAACAGGTTCTCCTTCCCCAGTCACCAAGTTGCTCGAGTTAGAATTGTCTGCA**ATG**GCC  
GCCCTGCAGAAATCTGTGAGCTCTTTCCCTTATGGGGACCCTGGCCACCAGCTGCCTCCTTCTC  
TTGGCCCTCTTGGTACAGGGAGGAGCAGCTGCGCCCATCAGCTCCCACTGCAGGCTTGACAAG  
TCCAACCTCCAGCAGCCCTATATCACCAACCGCACCTTCATGCTGGCTAAGGAGGCTAGCTTG  
GCTGATAACAACACAGACGTTCTGCTCATTGGGGAGAACTGTTCCACGGAGTCAGTATGAGT  
GAGCGCTGCTATCTGATGAAGCAGGTGCTGAACCTTCACCCTTGAAGAAGTGCTGTTCCCTCAA  
TCTGATAGGTTCCAGCCTTATATGCAGGAGGTGGTGCCCTTCCTGGCCAGGCTCAGCAACAGG  
CTAAGCACATGTCATATTGAAGGTGATGACCTGCATATCCAGAGGAATGTGCAAAAGCTGAAG  
GACACAGTGAAAAAGCTTGGAGAGAGTGGAGAGATCAAAGCAATTGGAGAACTGGATTTGCTG  
TTTATGTCTCTGAGAAATGCCTGCATT**TGA**CCAGAGCAAAGCTGAAAAATGAATAACTAACCC  
CCTTTCCTGCTAGAAATAACAATTAGATGCCCCAAAGCGATTTTTTTTAACCAAAGGAAGA  
TGGAAGCCAAACTCCATCATGATGGGTGGATTCCAAATGAACCCCTGCGTTAGTTACAAAGG  
AAACCAATGCCACTTTTGTTTATAAGACCAGAAGGTAGACTTTCTAAGCATAGATATTTATTG  
ATAACATTTTCATTGTAAGTGGTGTTCTATACACAGAAAACAATTTATTTTTTAAATAATTGTC  
TTTTTCCATAAAAAAGATTACTTTCATTCCCTTTAGGGGAAAAAACCCCTAAATAGCTTCATG  
TTTCCATAATCAGTACTTTATATTTATAAATGTATTTATTATTATTATAAGACTGCATTTTAT  
TTATATCATTTTATTAAATATGGATTTATTTATAGAAACATCATTCGATATTGCTACTTGAGTG  
TAAGGCTAATATTGATATTTATGACAATAATTATAGAGCTATAACATGTTTATTTGACCTCAA  
TAAACACTTGGATATCCC

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**FIGURE 154**

MAALQKSVSSFIMGTLATSCLLLLLALLVQGGAAAPISSHCRLDKSNFQQPYITNRTFMLAKEA  
SLADNNTDVRLIGEKLFHGVSMSERCYLMKQVLNFTLEEVLFQSDRFQPYMQEVVPFLARLS  
NRLSTCHIEGDDLHIQRNVQKLKDTVKKLGESGEIKAIGELDLLFMSLRNACI

**Important features of the protein:****Signal peptide:**

amino acids 1-33

**N-glycosylation sites.**

amino acids 54-58, 68-72, 97-101

**N-myristoylation sites.**

amino acids 14-20, 82-88

**Prokaryotic membrane lipoprotein lipid attachment site.**

amino acids 10-21

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**FIGURE 155**

GGCTTGCTGAAAATAAAATCAGGACTCCTAACCTGCTCCAGTCAGCCTGCTTCCACGAGGCCCT  
GTCAGTCAGTGCCCCGACTTGTGACTGAGTGTGCAGTGCCCAGCATGTACCAGGTCAGTGCAGA  
GGGCTGCCTGAGGGCTGTGCTGAGAGGGAGAGGAGCAGAGATGCTGCTGAGGGTGGAGGGAGG  
CCAAGCTGCCAGGTTTGGGGCTGGGGGCCAAGTGGAGTGAGAACTGGGATCCCAGGGGGAGG  
GTGCAGATGAGGGAGCGACCCAGATTAGGTGAGGACAGTTCTCTCATTAGCCTTTTCCTACAG  
GTGGTTGCATTCTTGGCAATGGTCATGGGAACCCACACCTACAGCCACTGGCCCAGCTGCTGC  
CCCAGCAAAGGGCAGGACACCTCTGAGGAGCTGCTGAGGTGGAGCACTGTGCCTGTGCCTCCC  
CTAGAGCCTGCTAGGCCCAACCGCCACCCAGAGTCCTGTAGGGCCAGTGAAGATGGACCCCTC  
AACAGCAGGGCCATCTCCCCCTGGAGATATGAGTTGGACAGAGACTTGAACCGGCTCCCCCAG  
GACCTGTACCACGCCCCTTGCCTGTGCCCCGCACTGCGTCAGCCTACAGACAGGCTCCACATG  
GACCCCCGGGGCAACTCGGAGCTGCTCTACCACAACCAGACTGTCTTCTACAGGCGGCCATGC  
CATGGCGAGAAGGGCACCCACAAGGGCTACTGCCTGGAGCGCAGGCTGTACCGTGTTCCTTA  
GCTTGTGTGTGTGTGCGGCCCCGTGTGATGGGCTAGCCGGACCTGCTGGAGGCTGGTCCCTTT  
TTGGGAAACCTGGAGCCAGGTGTACAACCACTTGCCATGAAGGGCCAGGATGCCCAGATGCTT  
GGCCCCGTGAAGTGCTGTCTGGAGCAGCAGGATCCCGGGACAGGATGGGGGGCTTTGGGGAA  
AACCTGCACTTCTGCACATTTTGAAAAGAGCAGCTGCTGCTTAGGGCCGCCGAAGCTGGTGT  
CCTGTCATTTTCTCTCAGGAAAGGTTTTCAAAGTTCTGCCCATTTCTGGAGGCCACCACTCCT  
GTCTCTTCCTCTTTTCCCATCCCCTGCTACCCTGGCCCAGCACAGGCACTTTCTAGATATTTT  
CCCCTTGCTGGAGAAGAAAGAGCCCCCTGGTTTTATTGTGTTGTTTACTCATCACTCAGTGAGC  
ATCTACTTTGGGTGCATTCTAGTGTAGTTACTAGTCTTTTGACATGGATGATTCTGAGGAGGA  
AGCTGTTATTGAATGTATAGAGATTTATCCAAATAAATATCTTTATTTAAAAATGAAAAA

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**FIGURE 156**

MRERPRLGEDSSLISLFLQVVAFLAMVMGTHYSHWPSCCPSKGQDTSEELLRWSTVPVPPLE  
PARPNRHPESCRASEDGPLNSRAISPWRYELDRDLNRLPQDLYHARCLCPHCVSLQTGSHMDP  
RGNSELLYHNQTVFYRRPCHGEKGTKGYCLERRLYRVSLACVCVRPRVMG

**Important features of the protein:****Signal peptide:**

amino acids 1-32

**N-glycosylation site.**

amino acids 136-140

**Tyrosine kinase phosphorylation site.**

amino acids 127-135

**N-myristoylation sites.**

amino acids 44-50, 150-156

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**FIGURE 157**

CCGGCG**ATG**TCGCTCGTGCTGCTAAGCCTGGCCGCGCTGTGCAGGAGCGCCGTACCCCGAGAG  
CCGACCGTTCAATGTGGCTCTGAAACTGGGCCATCTCCAGAGTGGATGCTACAACATGATCTA  
ATCCCCGGAGACTTGAGGGACCTCCGAGTAGAACCTGTTACAAC TAGTGTTGCAACAGGGGAC  
TATTCAATTTTGATGAATGTAAGCTGGGTACTCCGGGCAGATGCCAGCATCCGCTTGTTGAAG  
GCCACCAAGATTTGTGTGACGGGCAAAAGCAACTTCCAGTCCTACAGCTGTGTGAGGTGCAAT  
TACACAGAGGCCTTCCAGACTCAGACCAGACCCTCTGGTGGTAAATGGACATTTTCCTACATC  
GGCTTCCCTGTAGAGCTGAACACAGTCTATTTTCATTGGGGCCATAATATTCCTAATGCAAAT  
ATGAATGAAGATGGCCCTTCCATGTCTGTGAATTTACCTCACCAGGCTGCCTAGACCACATA  
ATGAAATATAAAAAAAGTGTGTCAAGGCCGGAAGCCTGTGGGATCCGAACATCACTGCTTGT  
AAGAAGAATGAGGAGACAGTAGAAGTGAACCTCACAAACCACTCCCCTGGGAAACAGATACATG  
GCTCTTATCCAACACAGCACTATCATCGGGTTTTCTCAGGTGTTTGAGCCACACCAGAAGAAA  
CAAACGCGAGCTTCAGTGGTGATTCCAGTGACTGGGGATAGTGAAGGTGCTACGGTGCAGCTG  
ACTCCATATTTTCCTACTTGTGGCAGCGACTGCATCCGACATAAAGGAACAGTTGTGCTCTGC  
CCACAAACAGGCGTCCCTTTCCCTCTGGATAACAACAAAAGCAAGCCGGGAGGCTGGCTGCCT  
CTCCTCCTGCTGTCTCTGCTGGTGGCCACATGGGTGCTGGTGGCAGGGATCTATCTAATGTGG  
AGGCACGAAAGGATCAAGAAGACTTCCTTTTCTACCACCACACTACTGCCCCCATTAAGGTT  
CTTGTGGTTTACCCATCTGAAATATGTTTCCATCACACAATTTGTTACTTCACTGAATTTCTT  
CAAAACCATTGCAGAAGTGAGGTCATCCTTGAAAAGTGGCAGAAAAAGAAAATAGCAGAGATG  
GGTCCAGTGCAGTGGCTTGCCACTCAAAAGAAGGCAGCAGACAAAGTCGTCTTCCTTCTTTCC  
AATGACGTCAACAGTGTGTGCGATGGTACCTGTGGCAAGAGCGAGGGCAGTCCCAGTGAGAAC  
TCTCAAGACCTCTTCCCCCTTGCCTTTAACCTTTTCTGCAGTGATCTAAGAAGCCAGATTCTAT  
CTGCACAAATACGTGGTGGTCTACTTTAGAGAGATTGATACAAAAGACGATTACAATGCTCTC  
AGTGTCTGCCCCAAGTACCACCTCATGAAGGATGCCACTGCTTTCTGTGCAGAACTTCTCCAT  
GTCAAGCAGCAGGTGTCAGCAGGAAAAAGATCACAAAGCCTGCCACGATGGCTGCTGCTCCTTG  
**TAG**

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**FIGURE 158**

MSLVLLSLAALCRSAVPREPTVQCGSETGPSPEWMLQHDLIIPGDLRLDLRVEPVTTTSVATGDYS  
ILMNVSWSVLRADASIRLLKATKICVTGKS NFQSYSCVRCNYTEAFQTQTRPSGGKWTFSYIGF  
PVELNTVYFIGAHNIPNANMNEDGPSMSVNFTSPGCLDHIMKYKKKCVKAGSLWDPNITACKK  
NEETVEVNFTTTPLGNRYMALIQHSTIIGFSQVFEPHQKKQTRASVVIPVTGDSEGATVQLTP  
YFPTCGSDCIRHKGTVVLCPTGVPFPLDNNKSKPGGWLPLLLLSLLVATWVLVAGIYLMWRH  
ERIKKTSFSTTTLLPPIKVLVVYPSEICFHHTICYFTEFLQNHCRSEVILEKWQKKKIAEMGP  
VQWLATQKKAADKVVFLLSNDVNSVCDGTGKSEGSPSENSQDLFPLAFNLFCSDLRSQIHLH  
KYVVVVFREIDTKDDYNALSVCPKYHLMKDATAFCAELLHVKQQVSAGKRSQACHDGCCSL

**Important features of the protein:****Signal peptide:**

amino acids 1-14

**Transmembrane domain:**

amino acids 290-309

**N-glycosylation sites.**amino acids 67 - 71, 103 - 107, 156 - 160, 183 - 187, 197 - 201  
and 283 - 287**cAMP- and cGMP-dependent protein kinase phosphorylation sites.**

amino acids 228 - 232 and 319 - 323

**Casein kinase II phosphorylation sites.**

amino acids 178 - 182, 402 - 406, 414 - 418 and 453 - 457

**N-myristoylation site.**

amino acids 116-122

**Amidation site.**

amino acids 488-452



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**FIGURE 159**

AGCCACCAGCGCAAC**ATG**ACAGTGAAGACCCTGCATGGCCCAGCCATGGTCAAGTACTTGCTG  
CTGTGATATTGGGGCTTGCCTTTCTGAGTGAGGCGGCAGCTCGGAAAATCCCCAAAGTAGGA  
CATACTTTTTTCCAAAAGCCTGAGAGTTGCCCGCCTGTGCCAGGAGGTAGTATGAAGCTTGAC  
ATTGGCATCATCAATGAAAACCAGCGCGTTTCCATGTCACGTAACATCGAGAGCCGCTCCACC  
TCCCCCTGGAATTACACTGTCACTTGGGACCCCAACCGGTACCCCTCGGAAGTTGTACAGGCC  
CAGTGTAGGAACTTGGGCTGCATCAATGCTCAAGGAAAGGAAGACATCTCCATGAATTCCGTT  
CCCATCCAGCAAGAGACCCTGGTCGTCCGGAGGAAGCACCAAGGCTGCTCTGTTTCTTTCCAG  
TTGGAGAAGGTGCTGGTGACTGTTGGCTGCACCTGCGTCACCCCTGTCATCCACCATGTGCAG  
**TAA**GAGGTGCATATCCACTCAGCTGAAGAAG

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## **FIGURE 160**

MTVKTLHGPMVKYLLLSILGLAFLSEAAARKIPKVGHTFFQKPESCPPVPGGSMKLDIGIIN  
ENQRVSMsrNIESRSTSPWNYTVTWDPNRYPSEVVQAQCRNLGCINAQGKEDISMNSVPIQQE  
TLVVRRKHQGCSVSFQLEKVLVTVGCTCVTPVIHHVQ

**Signal sequence:**

amino acids 1-30

**N-glycosylation site.**

amino acids 83-87

**N-myristoylation sites.**

amino acids 106-111, 136-141

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**FIGURE 161**

ACACTGGCCAAACAAAAACGAAAGCACTCCGTGCTGGAAGTAGGAGGAGAGTCAGGACTCCCA  
GGACAGAGAGTGCACAAACTACCCAGCACAGCCCCCTCCGCCCCCTCTGGAGGCTGAAGAGGG  
ATTCCAGCCCCCTGCCACCCACAGACACGGGCTGACTGGGGTGTCTGCCCCCCTTGGGGGGGG  
CAGCACAGGGCCTCAGGCCTGGGTGCCACCTGGCACCTAGAAGATGCTGTGCCCTGGTTCTT  
GCTGTCTTGGCACTGGGCCGAAGCCCACTGGTCTTCTCTGGAGAGGCTTGTGGGGCCTCA  
GGACGCTACCCACTGCTCTCCGGGCCCTCTCTGCCGCCTCTGGGACAGTGACATACTCTGCCT  
GCCTGGGGACATCGTGCCTGCTCCGGGCCCGTGTGGCGCCTACGCACCTGCAGACAGAGCT  
GGTGTGAGGTGCCAGAAGGAGACCGACTGTGACCTCTGTCTGCGTGTGGCTGTCCACTTGGC  
CGTGCATGGGCACTGGGAAGAGCCTGAAGATGAGGAAAAGTTTGGAGGAGCAGCTGACTCAGG  
GGTGGAGGAGCCTAGGAATGCCTCTCTCCAGGCCCAAGTCGTGCTCTCCTTCCAGGCCTACCC  
TACTGCCCCGTGCGTCTTGTGGAGGTGCAAGTGCCTGCTGCCCTTGTGCAGTTTGGTCAGTC  
TGTGGGCTCTGTGGTATATGACTGCTTCGAGGCTGCCCTAGGGAGTGAGGTACGAATCTGGTC  
CTATACTCAGCCCAGGTACGAGAAGGAACTCAACCACACACAGCAGCTGCCTGCCCTGCCCTG  
GCTCAACGTGTGAGCAGATGGTGACAACGTGCATCTGGTTCTGAATGTCTCTGAGGAGCAGCA  
CTTCGGCCTCTCCCTGTACTGGAATCAGGTCCAGGGCCCCCAAAACCCCGGTGGCACAAAAA  
CCTGACTGGACCGCAGATCATTACCTGAACCACACAGACCTGGTTCCTGCCTCTGTATTCA  
GGTGTGGCCTCTGGAACCTGACTCCGTTAGGACGAACATCTGCCCTTCAGGGAGGACCCCCG  
CGCACACCAGAACCTCTGGCAAGCCGCCGACTGCGACTGCTGACCCTGCAGAGCTGGCTGCT  
GGACGCACCGTCTGCTGCTGCCCGCAGAAGCGGCAGTGTGCTGGCGGGCTCCGGGTGGGGACCC  
CTGCCAGCACTGGTCCCACCGCTTTCCTGGGAGAACGTCACTGTGGACAAGGTTCTCGAGTT  
CCCATTGCTGAAAGGCCACCCTAACCTCTGTGTTCAAGGTGAACAGCTCGGAGAAGCTGCAGCT  
GCAGGAGTGCTTGTGGGCTGACTCCCTGGGGCCTCTCAAAGACGATGTGCTACTGTTGGAGAC  
ACGAGGCCCCCAGGACAACAGATCCCTCTGTGCCTTGGAAACCCAGTGGCTGTACTTCACTACC  
CAGCAAAGCCTCCACGAGGGCAGCTCGCCTTGGAGAGTACTTACTACAAGACCTGCAGTCAGG  
CCAGTGTCTGCAGCTATGGGACGATGACTTGGGAGCGCTATGGGCCTGCCCCATGGACAAATA  
CATCCACAAGCGCTGGGCCCTCGTGTGGCTGGCCTGCCTACTCTTTGCCGCTGCGCTTTCCT  
CATCCTCCTTCTCAAAAAGGATCACGCGAAAGGGTGGCTGAGGCTCTTGAAACAGGACGTCCG  
CTCGGGGGCGGCCGCCAGGGGCCGCGCGCTCTGCTCCTCTACTCAGCCGATGACTCGGGTTT  
CGAGCGCCTGGTGGGCGCCCTGGCGTCCGCCCTGTGCCAGCTGCCGCTGCGCGTGGCCGTAGA  
CCTGTGGAGCCGTCTGAACTGAGCGCGCAGGGGCCCGTGGCTTGGTTTACGCGCAGCGGCG  
CCAGACCCTGCAGGAGGGCGGCGTGGTGGTCTTGTCTTCTCTCCCGGTGCGGTGGCGCTGTG  
CAGCGAGTGGCTACAGGATGGGGTGTCCGGGCCCGGGCGCACGGCCCGCACGACGCCTTCCG  
CGCCTCGCTCAGCTGCGTGTGCCGACTTCTTGCAGGGCCGGGCGCCCGGCAGCTACGTGGG  
GGCCTGCTTCGACAGGCTGCTCCACCCGGACGCCGTACCCGCCCTTTTCCGCACCGTGCCCGT  
CTTCACACTGCCCTCCCAACTGCCAGACTTCTTGGGGGCCCTGCAGCAGCCTCGCGCCCCGCG  
TTCCGGGCGGCTCCAAGAGAGAGCGGAGCAAGTGTCCCGGGCCCTTCAGCCAGCCCTGGATAG  
CTACTTCCATCCCCCGGGGACTCCCGCGCCGGGACGCGGGGTGGGACCAGGGGCGGGACCTGG  
GGCGGGGGACGGGACTTAAATAAAGGCAGACGCTGTTTTTCTAAAAAA

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**FIGURE 162**

MPVPWFLLSLALGRSPVVLSLERLVGPQDATHCSPGLSCRLWDSILCLPGDIVPAPGPVLAP  
THLQTELVLRQCKETDCDLCLRVAVHLAVHGHWEPEDEEKFGGAADSGVEEPRNASLQAQVV  
LSFQAYPTARCVLLEVQVPAALVQFGQSVGSVVYDCFEAALGSEVRIWSYTQPRYEKELNHTQ  
QLPALPWLNVSADGDNVHLVLNVSEEQHFGLSLYWNQVQGPPKPRWHKNLTGPQIITLNHTDL  
VPCLCIQVWPLEPDSVRTNICPFREDPRAHQNLWQAARLRLTLQSWLLDAPCSLPAEAALCW  
RAPGGDPCQPLVPPLSWENVTVDKVLEFPLLKGHPNLCVQVNSSEKLQLQECLWADSLGPLKD  
DVLLLETRGPQDNRSLEPSGCTSLPSKASTRAARLGEYLLQDLQSGQCLQLWDDDLGALW  
ACPMDKYIHKRWALVWLACLLFAAALSLILLKKDHAKGWLRLKQDVRSGAAARGRAALLY  
SADDSGFERLVGALASALCQLPLRVAVDLWSRRELSAQGPVAVFHAQRRQTLQEGGVVLLFS  
PGAVALCSEWLQDGVSGPGAHGPHDAFRASLSCVLPDFLQGRAPGSYVGACFDRLLHPDAVPA  
LFRTVPVFTLPSQLPDFLGALQQPRAPRSGRLQERAEQVSRALQPALDSYFHPPGTPAPGRGV  
GPGAGPGAGDGT

**Signal sequence:**

amino acids 1-20

**Transmembrane domain.**

amino acids 453-475

**N-glycosylation sites.**amino acids 118-121, 186-189, 198-201, 211-214, 238-241, 248-251,  
334-337, 357-360, 391-394**Glycosaminoglycan attachment site.**

amino acids 583-586

**cAMP- and cGMP-dependent protein kinase phosphorylation site.**

amino acids 552-555

**N-myristoylation sites.**amino acids 107-112, 152-157, 319-324, 438-443, 516-521, 612-617,  
692-697, 696-701, 700-705

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**FIGURE 163**

GGGAGGGCTCTGTGCCAGCCCCG**ATG**AGGACGCTGCTGACCATCTTGACTGTGGGATCCCTGG  
CTGCTCACGCCCCTGAGGACCCCTCGGATCTGCTCCAGCACGTGAAATTCAGTCCAGCAACT  
TTGAAAACATCCTGACGTGGGACAGCGGGCCAGAGGGCACCCAGACACGGTCTACAGCATCG  
AGTATAAGACGTACGGAGAGAGGGACTGGGTGGCAAAGAAGGGCTGTCAGCGGATCACCCGGA  
AGTCCTGCAACCTGACGGTGGAGACGGGCAACCTCACGGAGCTCTACTATGCCAGGGTCACCGCT  
GTCAGTGCGGGAGGCCGGTCAGCCACCAAGATGACTGACAGGTTGAGTCTCTGTCAGCACACT  
ACCCTCAAGCCACCTGATGTGACCTGTATCTCCAAAGTGAGATCGATTGAGATGATTGTTTCAT  
CCTACCCCCACGCCAATCCGTGCAGGCGATGGCCACCGGCTAACCTGGAAGACATCTTCCAT  
GACCTGTTCTACCACTTAGAGCTCCAGGTCAACCGCACCTACCAAATGCACCTTGGAGGGAAG  
CAGAGAGAATATGAGTTCTTCGGCCTGACCCCTGACACAGAGTTCCCTTGGCACCATCATGATT  
TGCGTTCCACCTGGGCCAAGGAGAGTGCCCCCTACATGTGCCGAGTGAAGACACTGCCAGAC  
CGGACATGGACCTACTCCTTCTCCGGAGCCTTCCTGTTCTCCATGGGCTTCCTCGTCGCAGTA  
CTCTGTACCTGAGCTACAGATATGTACCAAGCCGCCTGCACCTCCCAACTCCCTGAACGTC  
CAGCGAGTCTGACTTTCCAGCCGCTGCGCTTCATCCAGGAGCACGTCTGATCCCTGTCTTT  
GACCTCAGCGCCCCCAGCAGTCTGGCCCAGCCTGTCCAGTACTCCAGATCAGGGTGTCTGGA  
CCCAGGAGCCCCGAGGAGCTCCACAGCGGCATAGCCTGTCCGAGATCACCTACTTAGGGCAG  
CCAGACATCTCCATCCTCCAGCCCTCCAACGTGCCACCTCCCCAGATCCTCTCCCCACTGTCC  
TATGCCCCAAACGCTGCCCCCTGAGGTGCGGGCCCCCATCTATGCACCTCAGGTGACCCCCGAA  
GCTCAATTCCCATTTCTACGCCCCACAGGCCATCTTAAGGTCCAGCCTTCCTCCTATGCCCCCT  
CAAGCCACTCCGGACAGCTGGCCTCCCTCCTATGGGGTATGCATGGAAGGTTCTGGCAAAGAC  
TCCCCCACTGGGACACTTTCTAGTCTTAAACCTTAGGCCCTAAAGGTCAGCTTCAGAAAGAC  
CCACCAGCTGGAAGCTGCATGTTAGGTGGCCTTTCTCTGCAGGAGGTGACCTCCTTGGCTATG  
GAGGAATCCCAAGAAGCAAAATCATTGCACCAGCCCCTGGGGATTTGCACAGACAGAACATCT  
GACCCAAATGTGCTACACAGTGGGGAGGAAGGGACACCACAGTACCTAAAGGGCCAGCTCCCC  
CTCCTCTCCTCAGTCCAGATCGAGGGCCACCCCATGTCCCTCCCTTTGCAACCTCCTTCCGGT  
CCATGTTCCCCCTCGGACCAAGGTCCAAGTCCCTGGGGCCTGCTGGAGTCCCTTGTGTGTCCC  
AAGGATGAAGCCAAGAGCCCAGCCCCTGAGACCTCAGACCTGGAGCAGCCCACAGAAGTGGAT  
TCTCTTTTCAGAGGCTGGCCCTGACTGTGCAGTGGGAGTCT**CGA**GGGGAATGGGAAAGGCTT  
GGTGCTTCCCTGCTCCCTACCCAGTGTACATCCTTGGCTGTCAATCCCATGCCTGCCCCAT  
GCCACACACTCTGCGATCTGGCCTCAGACGGGTGCCCTTGAGAGAAGCAGAGGGAGTGGCATG  
CAGGGCCCCCTGCCATGGGTGCGCTCCTCACCGGAACAAAGCAGCATGATAAGGACTGCAGCGG  
GGGAGCTCTGGGGAGCAGCTTGTGTAGACAAGCGCGTGCTCGCTGAGCCCTGCAAGGCAGAAA  
TGACAGTGCAAGGAGGAAATGCAGGGAACTCCCGAGGTCCAGAGCCCCACCTCCTAACACCA  
TGGATTCAAAGTGCTCAGGGAATTTGCCTCTCCTTGCCCCATTCTGGCCAGTTTCACAATCT  
AGCTCGACAGAGCATGAGGCCCTGCCTCTTCTGTGATTGTTCAAAGGTGGGAAGAGAGCCTG  
GAAAAGAACCAGGCCTGGAAAAGAACCAGAAGGAGGCTGGGCAGAACCAGAACACCTGCACT  
TCTGCCAAGGCCAGGGCCAGCAGGACGGCAGGACTCTAGGGAGGGGTGTGGCCTGCAGCTCAT  
TCCCAGCCAGGGCAACTGCCTGACGTTGCACGATTTAGCTTCATTCTCTGATAGAACAAG  
CGAAATGCAGGTCCACCAGGGAGGGAGACACACAAGCCTTTTCTGCAGGCAGGAGTTTCAGAC  
CCTATCCTGAGAATGGGGTTTGAAAGGAAGGTGAGGGCTGTGGCCCCTGGACGGGTACAATAA  
CACACTGTACTGATGTACAACTTTGCAAGCTCTGCCTTGGGTTCAGCCCATCTGGGCTCAAA  
TTCCAGCCTCACCCTCACAAGCTGTGTGACTTCAAACAAATGAAATCAGTGCCCAAGACCTC  
GGTTTCTCATCTGTAATGTGGGGATCATAACACCTACCTCATGGAGTTGTGGTGAAGATGAA  
ATGAAGTCATGTCTTTAAAGTGCTTAATAGTGCCTGGTACATGGGCAGTGCCCAATAACGGT  
AGCTATTTAAAAA

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**FIGURE 164**

MRTLLTILTVGSLAAHAPEDPSDLLQHVKFQSSNFENILTWDSGPEGTPDTVYSIEYKTYGER  
DWVAKKGCQRITRKSCNLTIVETGNLTELYARVTAVSAGGRSATKMTDRFSSLQHTTLKPPDV  
TCISKVRSIQMIVHPTPTPIRAGDGHRLTLEDIFHDLFYHLELQVNRTYQMHGGKQREYEFF  
GLTPDTEFLGTIMICVPTWAKESAPYMCRVKTLPDRTWTYSFSGAFLFSMGFLVAVLCYLSYR  
YVTKPPAPPNSLNVQRVLTFFQPLRFIQEHVLI PVFDLSGPSSLAQPVQYSQIRVSGPREPAGA  
PQRHSLSEITYLGQPDISILQPSNVPPPQILSPLSYAPNAAPEVGPPSYAPQVTPEAQFFFYA  
PQAISKVQPSSYAPQATPDSWPSPSYGVCMEGSGKDSPTGTLSSPKHLRPKGQLQKEPPAGSCM  
LGGLSLQEVTS LAMEESQEAKSLHQPLGICTDRTSDPNVLHSGEEGTPQYILKGQLPLLSSVQI  
EGHPMSLPLQPPSGPCSPSDQGSPWGGLLESIVCPKDEAKSPAPETSDLEQPTELDSLFRGLA  
LTVQWES

**Signal sequence.**

amino acids 1-17

**Transmembrane domain.**

amino acids 233-250

**N-glycosylation sites.**

amino acids 80-83, 87-90, 172-175

**N-myristoylation sites.**

amino acids 11-16, 47-52, 102-107, 531-536, 565-570

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**FIGURE 165**

TGGCCTACTGGAAAAAAAAAAAAAAAAAAAAAGTCACCCGGGCCCCGCGGTGGCCACAAC**AT**  
**GG**CTGCGGCGCCGGGGCTGCTCTTCTGGCTGTTTCGTGCTGGGGGCGCTCTGGTGGGTCCCGGG  
CCAGTCGGATCTCAGCCACGGACGGCGTTTCTCGGACCTCAAAGTGTCGGGGACGAAGAGTG  
CAGCATGTTAATGTACCGTGGGAAAGCTCTTGAAGACTTCACGGGCCCTGATTGTCGTTTTGT  
GAATTTTAAAAAGGTGACGATGTATATGTCTACTACAACTGGCAGGGGGATCCCTTGAAGT  
TTGGGCTGGAAGTGTTGAACACAGTTTTGGATATTTTCCAAAAGATTTGATCAAGGTACTTCA  
TAAATACACGGAAGAAGAGCTACATATTCCAGCAGATGAGACAGACTTTGTCTGCTTTGAAGG  
AGGAAGAGATGATTTTAATAGTTATAATGTAGAAGAGCTTTTAGGATCTTTGGAAGTGGAGGA  
CTCTGTACCTGAAGAGTCGAAGAAAGCTGAAGAAGTTTCTCAGCACAGAGAGAAATCTCCTGA  
GGAGTCTCGGGGCGTGAACCTTGACCCTGTGCCTGAGCCCGAGGCATTGAGAGCTGATTGAGA  
GGATGGAGAAGGTGCTTTCTCAGAGAGCACCGAGGGGCTGCAGGGACAGCCCTCAGCTCAGGA  
GAGCCACCCTCACACCAGCGGTCTGCGGCTAACGCTCAGGGAGTGCAGTCTTCGTTGGACAC  
TTTTGAAGAAATTCTGCACGATAAATTGAAAGTGCCGGGAAGCGAAAGCAGAACTGGCAATAG  
TTCTCCTGCCTCGGTGGAGCGGGAGAAGACAGATGCTTACAAAGTCCTGAAAACAGAAATGAG  
TCAGAGAGGAAGTGGACAGTGCCTTATTACATTACAGCAAAGGATTCGTTGGCATCAAATCT  
AAGTTTGTTTTACAAAGATTGTTTT**TAG**TACTAAGCTGCCTTGGCAGTTTGCATTTTTGAGCC  
AAACAAAATATATTATTTTCCCTTCTAAGTAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 166**

MAAAPGLLFWLFLVLGALWWVPGQSDLSHGRRFSDLKVCGDEEC SMLMYRGKALEDFTGPD CRF  
VNFKKGDDVYVYYKLAGGSLELWAGSVEHSFGYFPKDLIKVLHKYTEELHIPADETDFVC FE  
GGRDDFNSYNVEELLGSLELEDSVP EESKKAEEVSQHREKSP EESRGRELDPVPEPEAFRADS  
EDGEGAFSESTEG LQGQPSAQESH PHTSGPAANAQGVQSSLDTFEEILHDKLKVP GSESRTGN  
SSPASVEREKTDAYKVLKTEMSQRGSGQCVIHYSKGFRWHQNL SLFYKDCF

**Important features of the protein:****Signal peptide:**

amino acids 1-22

**N-glycosylation site.**

amino acids 294-298

**cAMP- and cGMP-dependent protein kinase phosphorylation site.**

amino acids 30-34

**Tyrosine kinase phosphorylation site.**

amino acids 67-76

**N-myristoylation sites.**

amino acids 205-211, 225-231, 277-283

**Amidation site.**

amino acids 28-32



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**FIGURE 167**

CCAGGACCAGGGCGCACCGGCTCAGCCTCTCACTTGTCTCAGAGGCCGGGGAAGAGAAGCAAAGC  
GCAACGGTGTGGTCCAAGCCGGGGCTTCTGCTTCGCCCTCTAGGACATACACGGGACCCCTAA  
CTTCAGTCCCCCAAACGCGCACCCCTCGAAGTCTTGAAGTCCAGCCCCGCACATCCACGCGCGG  
CACAGGCGCGGCAGGCGGCAGGTCCCGGCCGAAGGCGATGCGCGCAGGGGGTTCGGGCAGCTGG  
GCTCGGGCGGGGAGTAGGGCCCCGAGGGAGGCGAGGAGGCTGCATATTCAGAGTCGCGGG  
CTGCGCCCTGGGCAGAGGCCGCCCTCGCTCCACGCAACACCTGCTGCTGCCACCGCGCCGCGA  
**TA**GAGCCGCGTGGTCTCGCTGCTGCTGGGCGCCGCGCTGCTCTGCGGCCACGGAGCCTTCTGCC  
GCCGCGTGGTCAGCGGCCAAAAGGTGTGTTTTGCTGACTTCAAGCATCCCTGCTACAAAATGG  
CCTACTTCCATGAAGTGTCCAGCCGAGTGAGCTTTCAGGAGGCACGCCTGGCTTGTGAGAGTG  
AGGGAGGAGTCCTCCTCAGCCTTGAGAATGAAGCAGAACAGAAGTTAATAGAGAGCATGTTGC  
AAAACCTGACAAAACCCGGGACAGGGATTTCTGATGGTGATTTCTGGATAGGGCTTTGGAGGA  
ATGGAGATGGGCAAACATCTGGTGCCTGCCAGATCTCTACCAGTGGTCTGATGGAAGCAATT  
CCCAGTACCGAAACTGGTACACAGATGAACCTTCTGCGGAAGTGAAAAGTGTGTTGTGATGT  
ATCACCACCAACTGCCAATCCTGGCCTTGGGGGTCCCTACCTTTACCAGTGGAATGATGACA  
GGTGTAAACATGAAGCACAAATTATATTTGCAAGTATGAACCAGAGATTAATCCAACAGCCCCTG  
TAGAAAAGCCTTATCTTACAAATCAACCAGGAGACACCCATCAGAATGTGGTTGTTACTGAAG  
CAGGTATAATTCCCAATCTAATTTATGTTGTTATACCAACAATACCCCTGCTCTTACTGATAC  
TGGTTGCTTTTGGAACTGTTGTTTCCAGATGCTGCATAAAAGTAAAGGAAGAACAAAACTA  
GTCCAAACAGTCTACACTGTGGATTTCAAAGAGTACCAGAAAAGAAAGTGGCATGGAAGTAT  
**AA**TAACTCATTGACTTGGTTCAGAATTTTGTAACTCTGGATCTGTATAAGGAATGGCATCAG  
AACAATAGCTTGGAAATGGCTTGAAATCACAAGGATCTGCAAGATGAACTGTAAGCTCCCCCT  
TGAGGCAAATATTAAAGTAATTTTTATATGTCTATTATTTCAATTTAAAGAATATGCTGTGCTA  
ATAATGGAGTGAGACATGCTTATTTTGTAAAGGATGCACCCAACTTCAAACCTTCAAGCAA  
TGAAATGGACAATGCAGATAAAGTTGTTATCAACACGTCGGGAGTATGTGTGTTAGAAGCAAT  
TCCTTTTATTTCTTTACCTTTTCATAAGTTGTTATCTAGTCAATGTAATGTATATTGTATTGA  
AATTTACAGTGTGCAAAAGTATTTTACCTTTGCATAAGTGTGTTGATAAAAATGAACTGTTCTA  
ATATTTATTTTATGGCATCTCATTTTTCAATACATGCTCTTTTGATTAAAGAACTTATTAC  
TGTTGTCAACTGAATTCACACACACACAAATATAGTACCATAGAAAAAGTTTGTTTTCTCGAA  
ATAATTCATCTTTACGCTTCTCTGCTTTTGGTCAATGTCTAGGAAATCTCTTCAGAAATAAGA  
AGCTATTTTATTAAGTGTGATATAAACCTCCTCAAACATTTTACTTAGAGGCAAGGATTGTCT  
AATTTCAATTGTGCAAGACATGTGCCTTATAATTATTTTGTAGCTTAAAATTAACAGATTTTG  
TAATAATGTAACCTTTGTTAATAGGTGCATAAACACTAATGCAGTCAATTTGAACAAAAGAAGT  
GACATACACAATATAAATCATATGTCTTCACACGTTGCCATATAATGAGAAGCAGCTCTCTG  
AGGGTTCTGAAATCAATGTGGTCCCTCTCTTGCCCACTAAACAAAGATGGTTGTTTCGGGGTTT  
GGGATTGACACTGGAGGCAGATAGTTGCAAAGTTAGTCTAAGGTTTCCCTAGCTGTATTTAGC  
CTCTGACTATATTAGTATACAAAGAGGTGATGTGGTTGAGACCAGGTGAATAGTCACTATCAG  
TGTGGAGACAAGCACAGCACACAGACATTTTAGGAAGGAAAGGAACTACGAAATCGTGTGAAA  
ATGGGTTGGAACCATCAGTGATCGCATATTCATTGATGAGGGTTTGCTTGAGATAGAAAATG  
GTGGCTCCTTTCTGTCTTATCTCCTAGTTTCTTCAATGCTTACGCCTTGTTCTTCTCAAGAGA  
AAGTTGTAACCTCTCTGGTCTTCATATGTCCCTGTGCTCCTTTTAACCAAATAAAGAGTCTTG  
TTTCTGGGGGAA

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**FIGURE 168**

MSRVVSLLLGAALLCGHGAFCRRVVSQGKVCFADFKHPCYKMAYFHELSSRVSFQEARLACES  
EGGVLLSLENEAEQKLIESMLQNLTKPGTGISDGDWIGLWRNGDGQTSGACPDLYQWSDGSN  
SQYRNWYTDEPSCGSEKCVVMYHQPTANPGLGGPYLYQWDDRCNMKHNYICKYEPEINPTAP  
VEKPYLTNQPGDTHQNVVTEAGIIPNLIYVVIPTIPLLLLILVAFGTCCFQMLHKSkgRrTKT  
SPNQSTLWISKSTRKESGMEV

**Important features of the protein:****Signal peptide:**

amino acids 1-21

**Transmembrane domain:**

amino acids 214-235

**N-glycosylation sites.**

amino acids 86-89, 255-258

**cAMP- and cGMP-dependent protein kinase phosphorylation site.**

amino acids 266-269

**N-myristoylation sites.**

amino acids 27-32, 66-71, 91-96, 93-98, 102-107, 109-114, 140-145, 212-217